# EPA Reg. No. 11556-126
# Vol. 2

# Material to be added to a Mini-Jacket
(in the case where an e-Jacket exists)

Reg. No. 11556-126 (11556-REA)

## Send to SIG: check box ☑

This material is:

- ☑ New stamped-accepted label
- ☑ New CSF
- ☐ Notification
- ☐ Final Printed Label
- ☐ Other: New Registration

Instructions: Attach this notice on top of the material. It must be clipped all together and ~~there should be NO STAPLES in the material.~~ Then give the material with this coversheet to staff in the Information Services Center (Room 230).

Reviewer's Name: [signature]

Phone: 306-0415 Division: RD

Date: 12-11-07

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Registration Division (7505C)
1200 Pennsylvania Ave., N.W.
Washington, D.C. 20460

NOTICE OF PESTICIDE:
_X_ Registration
___ Reregistration

(under FIFRA, as amended)

| EPA Reg. Number: | Date of Issuance: |
|---|---|
| 11556-126 | DEC 11 2007 |

**Term of Issuance:**
From: December 11, 2007
To: December 11, 2008

**Name of Pesticide Product:**
Advantage Plus 9 for Cats

**Name and Address of Registrant (include ZIP Code):**

Bayer HealthCare LLC, Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

**Note:** Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is conditionally registered in accordance with FIFRA section 3(c)(7)(A) provided that you:

1. Within 1 year of the date of this letter, an acceptable Domestic Animal Safety study on kittens, using the approved formulation, must be received and approved by the Agency. This is a time-limited registration, therefore this registration will be allowed to expire on December 11, 2008 if an acceptable study is not submitted.

2. Submit and/or cite all data required for registration/reregistration/registration review of your product when the Agency requires all registrants of similar products to submit such data.

3. Make the following label changes before you release the product for shipment:
   a. Revise the EPA Registration Number to read, "*EPA Reg. No. 11556-126.*"
   b. Revise the claim "*Flea adulticide, larvicide, and ovicide*" to read "*Flea adulticide and ovicide.*"

**Signature of Approving Official:**

Venus Eagle, Product Manager (01)
Insecticide-Rodenticide Branch, Registration Division (7505P)

**Date:** DEC 11 2007

EPA Form 8570-6

c. Revise the label claim "*Kills adult fleas, larvae, and eggs*" to read "*Kills adult fleas and eggs.*"
d. The following claims are not appropriate for a cat label and must be deleted:
   - "*Remains effective after bathing and/or swimming*"
   - "*Remains effective following swimming and/or shampooing*"

4. The data requirements for storage stability (830-6317) and corrosion characteristics (830- 6320) have not been satisfied, and must be submitted within eighteen months of the date of this letter.

5. Submit one copy of the revised final printed label for the record before you release the product for shipment.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions.

A stamped copy of the label is enclosed for your records.

Venus Eagle
Product Manager (01)
Insecticide-Rodenticide Branch
Registration Division (7505P)

Enclosure

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

(Front Panel)



# Advantage® Plus 9

Topical Solution

Once-A-Month Topical Flea Treatment for Cats and Kittens 9 Weeks and Older and 9 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

- Available only through licensed practicing veterinarians
- For use on cats and kittens 9 weeks of age and older
- Advantage Plus contains [imidacloprid], and [an/the] [insect growth regulator] [IGR] [pyriproxyfen] [Nylar®]*
- A single topical application remains effective for at least 4 weeks
- Convenient, easy to apply topical solution
- Once a month topical flea treatment for cats 9 weeks of age or older
- Advantage Plus is indicated for the prevention and treatment of fleas on cats 9 weeks of age and older
- For the treatment and prevention of flea infestations
- One treatment prevents further flea infestations for at least 4 weeks
- Kills 98-100% of the fleas on cats within 12 hours and continues to prevent infestations for at least four weeks
- Kills fleas before they lay eggs
- Larval flea stages in the cat's surroundings are killed following contact with an Advantage Plus treated cat
- Kills larval stages of fleas in the pet's environment
- Kills 98-100% of fleas within 12 hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents reinfestations by killing adult fleas before they lay eggs
- Prevents flea eggs from hatching
- Effectively breaks the flea life cycle
- Effectively targets all [life] stages of [fleas]
- 3-way flea protection ([kills] [controls] adults, larvae, and eggs)
- Prevents flea eggs [and flea larvae] from developing into [(biting) (adult)] fleas
- Treatment with Advantage Plus rapidly kills fleas and may reduce the incidence of Flea Allergic Dermatitis [FAD]
- Flea adulticide, larvicide, and ovicide

- Prevents fleas on treated cats from infesting (reinfesting) your home
- Remains effective after bathing and/or swimming
- Remains effective following swimming and/or shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance (odor) free
- In child-resistant packaging

*NYLAR® - Registered trademark of McLaughlin Gormley King Co.

| Active Ingredients | % By Weight |
|---|---|
| Imidacloprid; [CAS 138261-41-3] | 9.10% |
| Pyriproxyfen; [CAS 95737-68-1] | 0.46% |
| Other Ingredients | 90.44% |
| Total | 100.00% |

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below for First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

## HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on kittens under 9 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-800-422-9874.

## FIRST AID

Have the product container or label with you when calling a poison control center or doctor, or going for treatment.

**IF SWALLOWED:** Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

**IF IN EYES:** Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

**IF ON SKIN:** Wash with plenty of soap and water.

**TO PHYSICIAN:** Treat the patient symptomatically.

([Four] [Six]) 0.014 fl. oz. (0.4 mL) Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-REA

Manufactured For

Bayer HealthCare LLC
Animal Health Division
PO Box 390
Shawnee Mission, Kansas 66201 USA

Made in Germany

(Back Panel)

# Advantage® Plus 9

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Cats and Kittens 9 Weeks and Older and 9 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, larvae, and eggs
- Waterproof
- In child-resistant packaging

READ ENTIRE LABEL BEFORE EACH USE

([Four] [Six]) 0.014 fl. oz. (0.4 mL) Tubes

(Inside Left Panel)

For the Prevention and Treatment of Flea Infestations on Cats and Kittens 9 Weeks and Older and 9 lbs and Under.

## DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

### HOW TO OPEN [4-Pack]

1. To open the blister, prepare blister card piece containing only one cavity/tube by cutting off a section of the blister card.
2. Do not cut close to the blister cavities.
3. Cut into the blister cavity across the small side close to the cap of the tube.
4. Peel off the cover foil and take out the tube.
5. Repeat steps 1 to 4 for each tube.

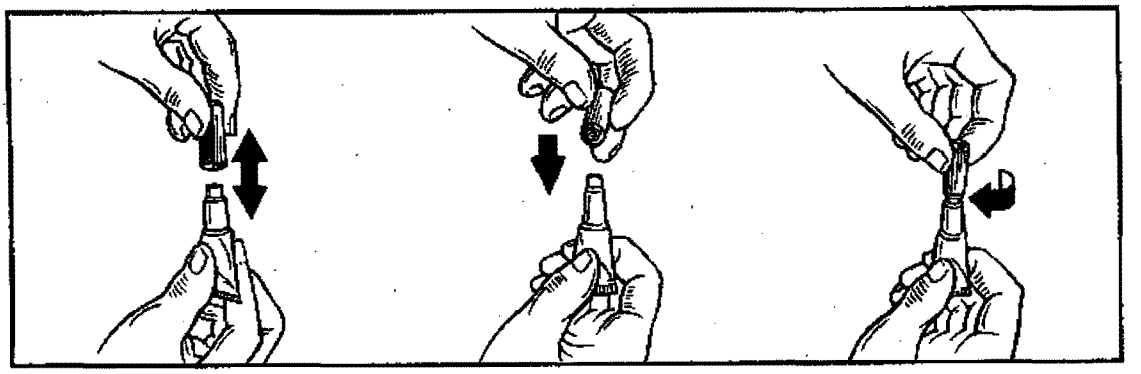
### HOW TO OPEN [6-Pack]

1. Take a pair of scissors and cut blister card in the center of the long side into two equal portions with 3 cavities/tubes each.
2. Do not cut close to the blister cavities.
3. The two halves of the blister card can now be separated into 3 pieces with one cavity/tube each.
4. To open the blister, prepare blister card piece containing only one cavity/tube.
5. Cut into the blister cavity across the small side close to the cap of the tube.
6. Peel off the cover foil and take out the tube.
7. Repeat steps 4 to 6 for each tube.

### HOW TO APPLY

1. Use only on cats. Do not use on other animals.

2. Remove one applicator tube from the package. See "HOW TO OPEN" section.

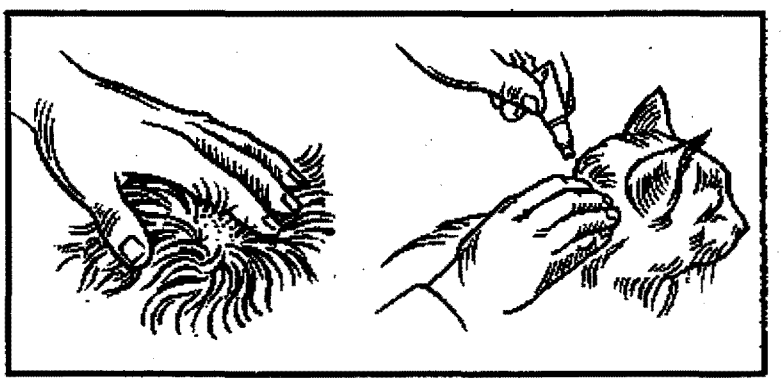


3. Hold applicator tube in an upright position. Pull cap off tube.

4. Turn the cap around and place other end of cap back on tube.

5. Twist cap to break seal, then remove cap from tube.

6. Part the hair in the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents of the tube directly on the skin. Do not get this product in your pet's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.



7. Discard empty tube as described in Storage and Disposal.

(Inside Right Panel)

Advantage® Plus 9

Topical Solution

Once-a-Month topical flea treatment for cats and kittens 9 weeks and older and 9 lbs. and under.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage® Plus rapidly kills fleas and reduces the incidence of this condition.

Advantage® Plus kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage® Plus treated pet. Advantage® Plus provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage® Plus kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® Plus is waterproof and remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

**If Empty**: Do not reuse this container. Place in trash or offer for recycling if available.
**If partly filled**: Call your local solid waste agency or (1-800-422-9874) for disposal instructions. Never place unused product down any indoor or outdoor drain.

## LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

**Doug Spilker**
**<doug.spilker.b@bayer.com>**

12/10/2007 04:38 PM

To Kable Davis/DC/USEPA/US@EPA

cc Venus Eagle/DC/USEPA/US@EPA, Dan Ciszewski <dan.ciszewski.b@bayer.com>, Terry McNamara <terry.mcnamara.b@bayer.com>,

bcc

Subject Advantage Plus 9 (EPA File Symbol 11556-REA) & Advantage Plus 18 (EPA File Symbol 11556-REO) on cats

Dear Mr. Davis,

Reference is made to the pending registrations for Advantage Plus 9 (EPA File Symbol 11556-REA) and Advantage Plus 18 (EPA File Symbol 11556-REO) on cats. We request the Agency grant Conditional Registrations for both pending products based on our commitment to do another domestic animal safety study on kittens, using the draft labels currently pending with the Agency. In order for the Conditional Registrations to be granted, we agree to submit the final report of the study within one (1) year of the Agency's acceptance of an appropriate protocol. To that end, we feel that the fastest way to reach such a agreement on an appropriate protocol for this study would be to have a meeting between our Target Animal Safety group and Mr. Byron Backus, Technical Review Branch.

If you need further information or clarification on this proposal, please call.

Best regards,

Doug

Doug Spilker Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
ANIMAL HEALTH
Office: +1 913-268-2751
Mobile: +1 816-506-3102
Fax: +1 913-268-2135
Email: doug.spilker.b@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Powered by People, Driven by Science"

Doug Spilker
<doug.spilker.b@bayer.com>

11/02/2007 11:10 AM

To Kable Davis/DC/USEPA/US@EPA
cc
bcc
Subject Revised Labels for Advantage Plus Cats (File Symbols 11556-REA, - REO)

Bo,
Both the attached labels, text dated 09/17/07, have had minor corrections made to them, and are outlined in the table below. These draft labels replace those on file and pending review for File Symbols 11556-REA and 11556-REO.

| Page | |
|---|---|
| 1 | Bullet 1 - reinserted word "only" in ethical statement;<br>Bullet 15 - removed "rapidly" per EPA comment on Adv Plus Dog labels.<br>Advantage Plus 18 only: Changed "....9 lbs and Over" to "....Over 9 lbs." |
| 2 | Replaced "Inert" with "Other in active ingredient statement. |
| 3 | Changed medical emergency number; added "Have product container...." statement under FIRST AID; added additional address line per EPA guidance. |
| 4 | No changes. |
| 5 | Added "s" to Infestation in heading. |
| 6 | No changes. |
| 7 | Added word "waterproof" in the shampooing/swimming statement (it already appears elsewhere) corrected STORAGE AND DISPOSAL statement according to PR 2001-6 |
| 8 | Revised Warranty Statement per EPA request |
| 9 | No changes |

Please call if you have questions or wish to discuss these labels.
best regards,
Doug

Doug Spilker Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
ANIMAL HEALTH
Office: +1 913-268-2751
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Fax: +1 913-268-2135
Email: doug.spilker.b@bayer.com

Address:

P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Powered by People, Driven by Science"




AdvantagePlus18d.pdf


AdvantagePlus9d.pdf

Form approved. OMB No. 2070-0060, 2070-0057, 2070-0107, 2070-0122, 2070-0164.

EPA

United States
**Environmental Protection Agency**
Washington, DC 20460

# Formulator's Exemption Statement

*(40 CFR 152.85)*

| Applicant's Name and Address | EPA File Symbol/Registration Number |
|---|---|
| Bayer HealthCare LLC<br>Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201 | 11556-REA |
| | Product Name<br>Advantage Plus 9 for Cats |
| | Date of Confidential Statement of Formula *(EPA Form 8570-4)*<br>03/08/2007 |

As an authorized representative of the applicant for registration of the product identified above, I certify that:

(1) This product contains the following active ingredient(s):

pyriproxyfen
imidacloprid (not citing Formulator's Exemption for this active ingredient)

(2) Of these, each active ingredient listed in paragraph (4) is present solely as the result of the use of that active ingredient in the manufacturing, formulation or repackaging another product which contains that active ingredient which is registered under FIFRA Section 3, is purchased by us from another person and meets the requirements of 40 CFR section 158.50(e)(2) or (3).

(3) Indicate by checking (A) or (B) below which paragraph applies:

☐ (A) An accurate Confidential Statement of Formula *(EPA FORM 8570-4)* for the above identified product is attached to this statement. That formula statement indicates, by company name, registration number, and product name, the source of the active ingredient(s) listed in paragraph (1).

**OR**

☑ (B) The Confidential Statement of Formula (CSF)(EPA Form 8570-4) referenced above and on file with the EPA is complete, current, an accurate and contains the information required on the current CSF.

(4) The following active ingredients in this product qualify for the formulator's exemption.

**Source**

| Active Ingredient | Product Name | Registration Number |
|---|---|---|
| pyriproxyfen | [redacted] | [redacted] |

| Signature | Name and Title | Date |
|---|---|---|
| | D.A. Spilker, EPA Reg. Affairs Mgr. | 09/14/2007 |

EPA Form 8570-27 (Rev. 06-2004)

Copy 1 – EPA
Copy 2 - Applicant copy

*Product ingredient source information may be entitled to confidential treatment*

Form Approved OMB Nos. 2070-0060; 2070-0057; 2070-0107; 2070-0122; 2070-0164

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**
**1200 Pennsylvania Avenue, N.W.**
**WASHINGTON, D.C. 20460**

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 1.25 hours per response for registration and 0.25 hours per response for reregistration and special review activities, including time for reading the instructions and completing the necessary forms. Send comments regarding burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden to: Director, Collection Strategies Division (2822T), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, N.W., Washington, DC 20460. Do not send the completed form to this address.

## Certification with Respect to Citation of Data

| | |
|---|---|
| Applicant's/Registrant's Name, Address, and Telephone Number<br>Bayer HealthCare LLC, Animal Health Div, POB 390, Shawnee Mission, KS 66201 [913-268-2751] | EPA Registration Number/File Symbol<br>11556-REA |
| Active Ingredient(s) and/or representative test compound(s)<br>pyriproxyfen, imidacloprid | Date<br>September 14, 2007 |
| General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 158)<br>Indoor, Non-food | Product Name<br>Advantage Plus 9 for Cats |

**NOTE:** If your product is a 100% repackaging of another purchased EPA-registered product labeled for all the same uses on your label, you do not need to submit this form. You must submit the Formulator's Exemption Statement (EPA Form 8570-27).

☐ I am responding to a Data-Call-In Notice, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

**SECTION I: METHOD OF DATA SUPPORT** (Check one method only)

| | |
|---|---|
| ☐ I am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose). | ☑ I am using the selective method of support (or cite-all option under the selective method), and have included with this form a completed list of data requirements (the Data Matrix form must be used). |

**SECTION II: GENERAL OFFER TO PAY**

[Required if using the cite-all method or when using the cite-all option under the selective method to satisfy one or more data requirements]

☑ I hereby offer and agree to pay compensation, to other persons, with regard to the approval of this application, to the extent required by FIFRA.

**SECTION III: CERTIFICATION**

I certify that this application for registration, this form for reregistration, or this Data-Call-In response is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-In response. In addition, if the cite-all option or cite-all option under the selective method is indicated in Section I, this application is supported by all data in the Agency's files that (1) concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses .

I certify that for each exclusive use study cited in support of this registration or reregistration, that I am the original data submitter or that I have obtained the written permission of the original data submitter to cite that study.

I certify that for each study cited in support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter; (b) I have obtained the permission of the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public literature; or (e) I have notified in writing the company that submitted the study and have offered (I) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.

I certify that in all instances where an offer of compensation is required, copies of all offers to pay compensation and evidence of their delivery in accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be submitted to the Agency upon request. Should I fail to produce such evidence to the Agency upon request, I understand that the Agency may initiate action to deny, cancel or suspend the registration of my product in conformity with FIFRA.

**I certify that the statements I have made on this form and all attachments to it are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.**

| Signature | Date | Typed or Printed Name and Title |
|---|---|---|
| Douglas A. Spilker | 09/14/2007 | Douglas A. Spilker, EPA Reg. Affairs Manager |

EPA Form 8570-34 (12-2003) Electronic and paper versions available. Submit only Paper version.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 0.25 hours per response for registration activities and .025 hours per response for information, including suggestions for reducing the burden to: Director, OPPE Information Management Division (2137), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Do not send the form to the address.

**DATA MATRIX**

| | | |
|---|---|---|
| **Date:** September 14, 2007 | **EPA Reg No./File Symbol:** 11556-REA, 11556-REO | Page 1 of 11 |
| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | **Product:** Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | **Ingredient:** Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |

| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Note<br>Report Number | Description |
|---|---|---|---|---|---|---|
| **Product Chemistry, Section 158.240** | | | | | | |
| 61-1 | Chemical identity | 42055302 | 264 | PER | BR 1759 (TGAI) | |
| | | 43306001 | 264 | PER | BR 1879 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 61-2 | Statement of Composition | 42055302 | 264 | PER | BR 1759 (TGAI) | |
| | | 43306001 | 264 | PER | BR 1879 (TGAI) | |
| | | 42270801 | 264 | PER | BR 1785 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 61-3 | Formation of impurities | 42055302 | 264 | PER | BR 1759 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 62-1 | Preliminary analysis | 42055303 | 264 | PER | BR 1760 (TGAI) | |
| | | 43306002 | 264 | PER | BR 1880 (TGAI) | |
| | | 42270802 | 264 | PER | BR 1786 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 62-2 | Certification of limits | 42055303 | 264 | PER | BR 1760 (TGAI) | |
| | | 43306002 | 264 | PER | BR 1880 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 62-3 | Analytical method | 42055303 | 264 | PER | BR 1760 (TGAI) | |
| | | 43213001 | 264 | PER | BR 1874 (TGAI) | |
| | | 43306002 | 264 | PER | BR 1880 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| | | 45096901 | 11556 | OWN | Report No. 75130 | Submitted with application for Advantage Plus 9 for Cats |

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 0.25 hours per response for registration activities and .025 hours per response for information, including suggestions for reducing the burden to: Director, OPPE Information Management Division (2137), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Do not send the form to the address.

**DATA MATRIX**

| | | |
|---|---|---|
| **Date:** September 14, 2007 | **EPA Reg No./File Symbol:** 11556-REA, 11556-REO | Page 2 of 11 |
| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | **Product:** Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | **Ingredient:** Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |

| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Note / Report Number | Description |
|---|---|---|---|---|---|---|
| 63-1 | Chemical and Physical Properties | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 63-2 | Appearance | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 63-3 | Physical state | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 63-4 | Odor | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 63-5 | Melting point | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| 63-6 | Boiling point | 42055304 | 264 | PER | BR 1761(TGAI) | |
| 63-7 | Density | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| | | 43356302 | 264 | PER | BR 1761 (Formulation) | |
| 63-8 | Solubility | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| 63-9 | Vapor pressure | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| 63-10 | Dissociation constant | | | | | N.A . - Does not dissociate |
| 63-11 | Octanol / water partition | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| 63-12 | pH | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| | | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 63-13 | Stability | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| 63-14 | Oxidizing / reducing action | | 264 | PER | | N.A. - No oxidative or reductive characteristics |
| 63-15 | Flammability | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| 63-16 | Explodability | 42055304 | 264 | PER | BR 1761 (TGAI) | |

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**DATA MATRIX**

| | | |
|---|---|---|
| **Date:** September 14, 2007 | **EPA Reg No./File Symbol:** 11556-REA, 11556-REO | Page 3 of 11 |
| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | **Product:** Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | **Ingredient:** Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |

| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Note / Report Number | Description |
|---|---|---|---|---|---|---|
| | | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| 63-17 | Storage stability | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 63-18 | Viscosity | | 264 | PER | | N.A. - Solid |
| 63-19 | Miscibility | | 264 | PER | | N.A. - Solid |
| | | 42055304 | 264 | PER | BR 1761 (TGAI) | |
| 63-20 | Corrosion characteristics | 42256302 | 264 | PER | BR 1766 (Formulation) | |
| 63-21 | Dielectric breakdown volt | | | | | N.A.- Solid |
| 64-1 | Submittal of samples | | | | Samples available upon request | |
| 830-Group A | Product Chemistry: Identity, Composition, Analysis | 45096902 | 11556 | OWN | Report No. 75133 | Submitted with application for Advantage Plus 9 for Cats |
| 830-Group B | Product Chemistry: Physical/Chemical Properties | 45096903 | 11556 | OWN | Report No. 75132 | Submitted with application for Advantage Plus 9 for Cats |
| **Wildlife and Aquatic Organisms, Section 158.490** | | | | | | |
| 71-1 | Acute avian oral - quail/duck | | | | | N.A. |
| 71-2(a) | Avian dietary - quail | | | | | N.A. |
| 71-2(b) | Avian dietary - duck | | | | | N.A. |
| 71-3 | Wild mammal toxicity | | | | | N.A. |
| 71-4(a) | Avian reproduction - quail | | | | | N.A. |
| 71-4(b) | Avian reproduction – duck | | | | | N.A. |
| 71-5 | Simulated or actual field study | | | | | N.A. |
| 72-1(a) | Fish toxicity - bluegill | | | | | N.A. |
| 72-1(b) | Fish toxicity bluegill - tep | | | | | N.A. |

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| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | **Product:** Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | **Ingredient:** Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |

| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Note<br>Report Number | Description |
|---|---|---|---|---|---|---|
| 72-2(a) | Invertebrate toxicity - Daphnia | | | | | N.A. |
| 72-2(b) | Invertebrate toxicity - Amphipods | | | | | N.A. |
| 72-2(c) | Acute aquatic invertebrate toxicity - Chironomids | | | | | N.A. |
| 72-3(a) | Estuarine / marine toxicity - fish | | | | | N.A. |
| 72-3(b) | Estuarine / marine toxicity - mollusk | | | | | N.A. |
| 72-3(c) | Estuarine/marine toxicity - shrimp | | | | | N.A. |
| 72-4(a) | Early life stage - fish | | | | | N.A. |
| 72-4(b) | Life cycle invertebrate | | | | | N.A. |
| 72-7 | Simulated or actual field study | | | | | N.A. |
| None | Foliar half-life and distribution for potatoes | | | | | N.A. |
| None | Runoff and Erosion predictions for apple/potato/cotton | | | | | N.A. |
| None | Risk assessment for apple/potato/cotton | | | | | N.A. |
| None | PELMO Modeling - sugarbeet/Germany | | | | | N.A. |
| **Toxicology, Section 158.340** | | | | | | |
| | | 42055331 | 264 | PER | Report No. 100040 (TGAI) | |
| | | 42256313 | 264 | PER | Report No. 100010 (2 F) | |
| | | 43428201 | 264 | PER | Report No. 106380 (1.6 F) | |
| | | 43679601 | 11556 | OWN | Report No. 74585 (Adv) | |
| | | 45096904 | 11556 | OWN | Report No. 75195 (Adv Plus) | Submitted with application for Advantage Plus 9 for Cats |
| 81-1 | Acute oral toxicity rat | 47089411 | 11556 | OWN | Report No. 75922 (Adv Plus) | Submitted with application for Advantage Plus 9 for Cats |

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| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | **Product:** Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | **Ingredient:** Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |

| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Note: Report Number | Note: Description |
|---|---|---|---|---|---|---|
| | | 42055332 | 264 | PER | Report No. 100041 (TGAI) | |
| | | 42256315 | 264 | PER | Report No. 100002 (2 F) | |
| | | 43428201 | 264 | PER | Report No. 106380 (1.6 F) | |
| | | 4379602 | 11556 | OWN | Report No. 74584 (Adv) | |
| 81-2 | Acute dermal toxicity, rat/rabbit | 45096905 | 11556 | OWN | Report No. 75196 | Submitted with application for Advantage Plus 9 for Cats |
| | | 42055333 | 264 | PER | Report No. 99806 (TGAI) | |
| | | 42286101 | 264 | PER | Report No. 99806-1 (TGAI) | |
| | | 42256317 | 264 | PER | Report No. 100012 (2 F) | |
| | | 43428201 | 264 | PER | Report No. 106380 (1.6 F) | |
| | | 43679603 | 11556 | OWN | Report No. 74589 (Adv) | |
| 81-3 | Acute inhalation toxicity, rat | 45096906 | 11556 | OWN | Report No. 75197 (Adv Plus) | Submitted with application for Advantage Plus 9 for Cats |
| | | 42055334 | 264 | PER | Report No. 99679 (TGAI) | |
| | | 42256319 | 264 | PER | Report No. 99815 (2 F) | |
| | | 43428201 | 264 | PER | Report No. 106380 (1.6 F) | |
| | | 43428201 | 264 | PER | Report No. 106380 (1.6 F) | |
| | | 43679604 | 11556 | OWN | Report No. 74588 (Adv) | |
| 81-4 | Primary eye irritation - rabbit | 45096907 | 11556 | OWN | Report No. 75199 (Adv Plus) | Submitted with application for Advantage Plus 9 for Cats |

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| Date: September 14, 2007 | | | EPA Reg No./File Symbol: 11556-REA, 11556-REO | | | Page 6 of 11 |
| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | | | Product: Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | | | Ingredient: Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |
| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Name<br>Report Number | Description |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 42055335 | 264 | PER | Report No. 99804 (TGAI) | |
| | | 42256321 | 264 | PER | Report No. 99816 (2 F) | |
| | | 43428201 | 264 | PER | Report No. 106380 (1.6 F) | |
| | | 43679605 | 11556 | OWN | Report No. 74586 (Adv) | |
| 81-5 | Primary dermal irritation - rabbit | 45096908 | 11556 | OWN | Report No. 75200 (Adv Plus) | Submitted with application for Advantage Plus 9 for Cats |
| | | 42055336 | 264 | PER | Report No. 99800 (TGAI) | |
| | | 42256323 | 264 | PER | Report No. 100003 (2 F) | |
| | | 43428201 | 264 | PER | Report No. 106380 (1.6 F) | |
| | | 43679606 | 11556 | OWN | Report No. 74587 (Adv) | |
| 81-6 | Dermal sensitization - guinea pig | 45096909 | 11556 | OWN | Report No. 75201 (Adv Plus) | Submitted with application for Advantage Plus 9 for Cats |
| | | 43170301 | 264 | PER | Report No. 106348 | |
| 81-8(SS) | Acute neurotoxicity | 43285801 | 264 | PER | Report No. 106348-1 | |
| 82-1(a) | 90-day feeding - rodent | 42256327 | 264 | PER | Report No. 100036 | |
| 82-1(b) | 90-day feeding - non-rodent | 42256328 | 264 | PER | Report No. 100176 | |
| 82-2 | 21-day dermal - rabbit/rat | 42256329 | 264 | PER | Report No. 100688 | |
| 82-5(b) | 90 day neurotoxicity - mammal | 43286401 | 264 | PER | Report No. 106356 | |
| | | 42256331 | 264 | PER | Report No. 100652 | |
| | | 42256332 | 264 | PER | Report No. 101931 | |
| | | 42256333 | 264 | PER | Report No. 102658 | |
| 83-1(a) | Chronic feeding toxicity - rodent | 42256334 | 264 | PER | Report No. 99672 | |

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| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | **Product:** Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | **Ingredient:** Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |

| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Note / Report Number | Description |
|---|---|---|---|---|---|---|
| 83-1(b) | Chronic feeding toxicity - non-rodent | 42273002 | 264 | PER | Report No. 100015 | |
| 83-2(a) | Oncogenicity - rat | 42256331 | 264 | PER | Report No. 100652 | |
| | | 42256332 | 264 | PER | Report No. 101931 | |
| | | 42256333 | 264 | PER | Report No. 102658 | |
| | | 42256334 | 264 | PER | Report No. 99672 | |
| 83-2(b) | Oncogenicity - mouse | 42256335 | 264 | PER | Report No. 100693 | |
| | | 42256336 | 264 | PER | Report No. 101929 | |
| | | 42256337 | 264 | PER | Report No. 99808 | |
| 83-3(a) | Developmental toxicity - rat | 42256338 | 264 | PER | Report No. 98571 | |
| 83-3(b) | Developmental toxicity - rabbit | 42256339 | 264 | PER | Report No. 98572 | |
| 83-4 | Two generation reproduction - rat | 42256340 | 264 | PER | Report No. 100647 | |
| 84-2(a) | Gene mutation (ames test) | 42256341 | 264 | PER | Report No. 101276 | |
| | | 42256342 | 264 | PER | Report No. 98584 | |
| | | 42256343 | 264 | PER | Report No. 98570 | |
| 84-2(b) | Structural chromosomal aberration | 42256344 | 264 | PER | Report No. 100021 | |
| | | 42256345 | 264 | PER | Report No. 99262 | |
| | | 42256346 | 264 | PER | Report No. 99257 | |
| | | 42256347 | 264 | PER | Report No. 102652 | |
| | | 42256348 | 264 | PER | Report No. 102654 | |
| | | 42256349 | 264 | PER | Report No. 102655 | |

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| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | **Product:** Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | **Ingredient:** Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |

| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Note / Report Number | Description |
|---|---|---|---|---|---|---|
| | | 42256350 | 264 | PER | Report No. 99676 | |
| | | 42256351 | 264 | PER | Report No. 101275 | |
| | | 42256352 | 264 | PER | Report No. 98573 | |
| 84-4 | Other genotoxic effects | 42256353 | 264 | PER | Report No. 102653 | |
| | | 42256354 | 264 | PER | Report No. 101999 | |
| | | 42256355 | 264 | PER | Report No. 87264 | |
| | | 42256356 | 264 | PER | Report No. 87265 | |
| 85-1 | General metabolism | 42256357 | 264 | PER | Report No. 102617 | |
| | | 43679501 | 11556 | OWN | Report No. 74579 (Adv) | Cats |
| | | 43679502 | 11556 | OWN | Report No. 74591 (Adv) | Cats |
| | | 44157301 | 11556 | OWN | Report No. 74746 (Adv) | Kittens |
| | | 44157302 | 11556 | OWN | Report No. 74747 (Adv) | Kittens |
| | | 45097001 | 11556 | OWN | Report No. 75122 (Adv Plus) | Cats, submitted with application for Advantage Plus 9 for Cats |
| | | 47089401 | 11556 | OWN | Report No. 75120 (Adv Plus) | Kittens, submitted with application for Advantage Plus 9 for cats |
| | | 47089402 | 11556 | OWN | Report No. 75120-1 (Adv Plus) | Addendum to Report No. 75120 |
| | | 47089403 | 11556 | OWN | Report No. 75190 (Adv Plus) | Kittens, submitted with application for Advantage Plus 9 for cats |
| | | 47089404 | 11556 | OWN | Report No. 75190-1 (Adv Plus) | Addendum to Report No. 75190 |
| 870.7200 | | 47089405 | 11556 | OWN | Report No. 75191 (Adv Plus) | Kittens, submitted with application for Advantage Plus 9 for cats |
| (86-1) | Domestic Animal Safety | 47089406 | 11556 | OWN | Report No. 75191-1 (Adv Plus) | Addendum to Report No. 75191 |

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| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | **Product:** Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | **Ingredient:** Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |

| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Note / Report Number | Description |
|---|---|---|---|---|---|---|
| | | 43679503 | 11556 | OWN | Report No. 74571 (Adv) | Cats |
| | | 43679504 | 11556 | OWN | Report No. 74581 (Adv) | Cats |
| | | 43679609 | 11556 | OWN | Report No. 74572 (Adv) | Dogs |
| | | 43679610 | 11556 | OWN | Report No. 74541 (Adv) | Dogs |
| | | 44256901 | 11556 | OWN | Report No. 74800 (Adv) | Speed of flea kill |
| | | 44256902 | 11556 | OWN | Report No. 47828 (Adv) | Larvicidal efficacy |
| | | 44256903 | 11556 | OWN | Report No. 74792 (Adv) | Effects of shampooing |
| | | 47109101 | 11556 | OWN | Report No.75867 (K9) | Waterproof |
| | | 45086801 | 1021 | PER | Report No. OT018-94 | Pyriproxyfen efficacy |
| | | 45086801 | 1021 | PER | Report No. OT016-93 | Pyriproxyfen efficacy |
| 95-9 | Efficacy | 45086801 | 1021 | PER | Report No. OT006-96 | Pyriproxyfen efficacy |
| **Plant Protection, Section 158.540** | | | | | | |
| 122-2 | Aquatic plant growth | | | | | N.A. |
| 123-2 | Aquatic plant growth | | | | | N.A. |
| **Non-Target Insects, Section 158.590** | | | | | | |
| 141-1 | Honey bee acute contact | | | | | N.A. |
| 141-2 | Honey bee residue on foliage | | | | | N.A. |
| **Reentry Protection, Section 158.390** | | | | | | |
| 230-236 | Mixer/loader/applicator exposure | | | | | N. A. |
| **Environmental Fate, Section 158.290** | | | | | | |
| 161-1 | Hydrolysis | | | | | N.A. |
| 161-2 | Photodegradation - water | | | | | N.A. |
| 161-3 | Photodegradation - soil | | | | | N.A. |

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| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | **Product:** Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | **Ingredient:** Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |

| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Note / Report Number | Description |
|---|---|---|---|---|---|---|
| 162-1 | Aerobic soil metabolism | | | | | N.A. |
| 162-2 | Anerobic soil metabolism | | | | | N.A. |
| 162-3 | Anaerobic aquatic metabolism | | | | | N.A. |
| 163-1 | Leaching / adsorption/desorption | | | | | N.A. |
| 164-1 | Terrestrial field dissipation | | | | | N.A. |
| 165-1 | Confined rotational crop | | | | | N.A. |
| 165-2 | Field rotational crop | | | | | N.A. |
| 166-1 | Ground water – small prospective | | | | | N.A. |
| None | Environmental fate summary | | | | | N.A. |
| **Residue, Section 158.240** | | | | | | |
| 171-4(a) | Nature of residue – plants | | | | | N.A. |
| 171-4(b) | Nature of residue – livestock and poultry | | | | | N.A. |
| 171-4© | Residue analytical method – plants | | | | | N.A. |
| 171-4(d) | Residue analytical method – animal | | | | | N.A. |
| 171-4(e) | Storage stability | | | | | N.A. |
| 171-4(j) | Magnitude of residues – meat/milk/poultry/egg | | | | | N.A. |
| 171-4(k) | Magnitude of residue – crop field trials | | | | | N.A. |
| 171-4(l) | Magnitude of residue – processed food/feed | | | | | N.A. |
| 171-4(m) | Method validation/ multiresidue method | | | | | N.A. |
| None | Benefits Reports | | | | | |
| None | Dietary Analysis | | | | | N.A. |

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| Bayer HealthCare LLC, Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201-0390 | **Product:** Advantage® Plus 9 for Cats<br>Advantage® Plus 18 for Cats | **Ingredient:** Imidacloprid, CAS = 138261-41-3<br>Pyriproxyfen, CAS = 95737-68-1 |

| Guideline Reference Number | Guideline Study Name | MRID Number | Submitter | Status | Note / Report Number | Description |
|---|---|---|---|---|---|---|
| **Child-Resistant Packaging, Section 157** | | | | | | |
| 157.20 | Standards – Child-Resistant Packaging Testing | 47089407 | 11556 | OWN | Report No. 75913 | Submitted with Advantage Plus 9 for Cats; 0.4 mL/4pk/Child |
| | | 47089408 | 11556 | OWN | Report No. 75914 | Submitted with Advantage Plus 9 for Cats; 0.4 mL/4pk/Adult |
| | | 47089409 | 11556 | OWN | Report No. 75915 | Submitted with Advantage Plus 9 for Cats; 0.4 mL/6pk/Child |
| | | 47089410 | 11556 | OWN | Report No. 75916 | Submitted with Advantage Plus 9 for Cats; 0.4 mL/6pk/Adult |
| | | 47089103 | 11556 | OWN | Report No. 75897 | Submitted with Advantage Plus 20 for Dogs; 1.0 mL/4pk/Child |
| | | 47089104 | 11556 | OWN | Report No. 75898 | Submitted with Advantage Plus 20 for Dogs; 1.0 mL/4pk/Adult |
| | | 47089101 | 11556 | OWN | Report No. 75893 | Submitted with Advantage Plus 20 for Dogs; 1.0 mL/6pk/Child |
| | | 47089102 | 11556 | OWN | Report No. 75894 | Submitted with Advantage Plus 20 for Dogs; 1.0 mL/6pk/Adult |

| Signature | Douglas A. Spilker<br>Manager, EPA Regulatory Affairs | September 14, 2007 |
|---|---|---|

EPA Form 8570-35 (9-97) Electronic Paper versions available. Submit only Paper version. Agency Internal Use Copy

# Bayer HealthCare
## Animal Health Division

November 12, 2007

Document Processing Desk (Additional Information/No Reg Fee)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle – Registration Division (7505P)

Subject: Adverse Effects [6(a) (2)] Follow-up
Advantage Products

Dear Ms. Eagle:

Bayer HealthCare LLC
Animal Health Division
12707 Shawnee Mission Parkway
Shawnee Mission, KS 66216-1846

This letter and the attached information are to allay the concerns expressed by the Agency during our meeting of November 1, 2007, regarding Bayer's completeness of Adverse Effects reporting. This information is in addition to the documents provided to you with our letter and attachments, dated November 2, 2007.

Bayer HealthCare, Animal Health Division, as well as Bayer Corporation in general, takes pharmacovigilance and adverse effects reporting very seriously, and has created a highly structured tracking system and organization that continues to be refined as new technologies and regulations develop. Although Bayer has been making timely submissions of 6(a) (2) reports to the Agency since the first registrations of the Advantage products (1996), our electronic tracking system, which is searchable, did not start until January 1, 1998. Consequently, we presented the information only from the searchable database, which is from the most recent 9½ years on the market (January 1, 1998 to June 30, 2007.)

With the documents attached and the previous documents provided on November 2, 2007, you have copies of our 6(a)(2) submissions for the time period (January 1, 1998 – June 30, 2007) covered in our November 1, 2007 presentation regarding cat/kitten incidents with Advantage.

Following our November 1 meeting, Bayer was provided with copies of the Agency's two documents titled "Advantage Incidents in IDS for 11556-116" and "Advantage Incidents in IDS for 11556-116-118," both dated 10/31/2007, and which both have a search date range of 1/1/92 – 9/21/2007. The domestic animal incidents cited in these searches, derived from your records for the two

Advantage cat products (11556-116) and (11556-118), is 2977 (1203 plus 1774, respectively). The Domestic Animal Fatality (D-A) total for the aforementioned two products was 118 (64 plus 54, respectively).

In our presentation on November 1, 2007, Bayer cited a total of 3329 cat/kitten incidents and 168 cat/kitten fatalities. The totals used in our presentation were derived by searching the database for incidents involving all cats and kittens involving Advantage **regardless** of whether the particular product was a cat product, a dog product, or an unspecified Advantage product. Please note that the Agency's search includes only the cat specific products (i.e. by Registration Number), and does not reflect: a) additional incidents where a Advantage dog product (which would have a different Registration Number) was used on cats, or b) additional cat incidents where the Advantage product was unspecified (i.e. had no Registration Number associated with it).

With regard to how these compare with the incident totals reported to the Agency as possible 6(a)(2) incidents, the following analysis can be done from the enclosed letters (covering the time period from January, 1998 through November, 1998) and the quarterly reports provided with our November 2, 2007 submission on this matter (these quarterly reports cover the time period from December, 1998 through June, 2007).

The enclosed letters contain a total of 345 cat/kitten incidents. The quarterly reports contain a total of 985 incidents for Advantage 9 (EPA Reg. No. 11556 – 116), a total of 1635 cat/kitten incidents for Advantage 18 (EPA Reg. No. 11556 – 118), and a total of 435 animal incidents with unspecified Advantage products. The resulting total is 345 + 985 + 1635 + 435 = 3400.

This number could be further refined by removing the number of incidents involving dogs in the animal incidents with unspecified Advantage products (there were 88 of these), by removing the number of incidents reported for dogs treated with an Advantage cat product (there were 31 of these), and by adding the number of incidents involving cats/kittens treated with an Advantage dog product (there were 163 of these). So, a refined total of cat/kitten incidents is 3400 – 88 – 31 + 163 = 3444.

Either of the two totals above correlate well with the 3329 cat/kitten incidents cited in our November 1 presentation; if anything, they are slightly greater.

With regard to the total number of cat/kitten fatalities in our 6(a)(2) reports, there were 26 cat/kitten deaths in the enclosed letters for the period from January, 1998 through November, 1998. The quarterly reports (covering December, 1998 through June 2007) contained 45 D - A's for Advantage 9 (EPA Reg. No. 11556 – 116), 47 D – A's for Advantage 18 (EPA Reg. No. 11556 -118), and 30 D –A's for animal deaths with unspecified Advantage

products. The resulting total is 26 + 45 + 47 + 30 = 148. We have also determined during further analysis of the database that in 15 cases, death occurred, but this was not reported to Bayer until some time after the initial incident report. In these instances, the incidents were reported based on the initial report and symptoms, but were not reported as fatalities (D – A) to the Agency. In these instances we have not attempted to file subsequent or some type of amended reports on these animals. When these 15 cases are added to the 148 total from above, there are 163 cases. When we include 17 cat fatality cases where an Advantage dog product was implicated (in the quarterly reports), our total fatality count is 180. In our analysis on November 1 the number was 168. Please note however, in the 180 total, this assumes all the D – A animal fatalities reported for unspecified Advantage products (where species is unknown) are cat/kitten, and we know at least some of these, but an undeterminable number, were dog fatalities.

As we related in our presentation, the analysis by organ type cannot be readily correlated by 6(a)(2) report because the analysis was done by searching the database with the various key words for the various organ systems. Consequently for example, if there was an incident where a cat displayed possible adverse effects with three different organ systems, this particular incident would have been included in the totals for each of the three organ systems resulting in an overall "triple" counting if all organ systems are added together.

In summary, it is apparent for many reasons that it is difficult to prepare in a short time a perfect correlation of the results of our computerized assessment (November 1, 2007 presentation) with the information sent to the Agency over that time period. Nonetheless, there is very good correlation in both number of incidents and number of fatality reports on cats/kittens. Furthermore, if anything, the total incidents reported to the Agency in that time are a little higher.

We hope this information is helpful, and that we have alleviated your concerns regarding our adverse effects reporting and the safe use of Advantage on cats and kittens. If you need anything further or have other questions, please do not hesitate to call (913-268-2751).

Sincerely,

Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs

FTM/DAS/das

Enclosures:

a) 6(a)(2) reports 1/1/1998 thru 11/30/1998

CC: Ms. M. Laws - EPA
Mr. K. Davis – EPA

Adv AE Follow up 11122007.doc

# Bayer HealthCare
## Animal Health Division

November 12, 2007

Document Processing Desk (Additional Information/No Reg Fee)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle – PM 01

Subject: Advantage Plus 9 (EPA File Symbol 11556-REA)
Advantage Plus 18 (EPA File Symbol 11556-REO)

Dear Ms. Eagle:

Bayer HealthCare LLC
Animal Health Division
12707 Shawnee Mission Parkway
Shawnee Mission, KS 66216-1846

In our November 1, 2007 meeting with the Agency on the subject pending registrations, Bayer representatives responded to a question regarding findings in the cerebellar external granular layer of tissue in kittens from the domestic animal safety studies. The Bayer representatives committed in the aforementioned meeting to provide more details and appropriate literature citations regarding this issue.

Accordingly, please find enclosed as Attachment 1 a brief summary regarding the kittens in question (those with the external granular findings) and a brief summary of the veterinary literature regarding the external granular layer. Enclosed as Attachment 2 is a report from a pathologist (B. P. Stuart, DVM, PhD, DACVP) of a contemporary review and opinion regarding the cerebellar histopathology slides from the kittens in question. Lastly, enclosed as Attachment 3 are copies of eight (8) scientific references describing the origin, importance and fate of the external granular cell layer in altricial mammals (particularly humans, puppies and kittens).

We hope this additional information is helpful in answering this issue, and will allow the Agency to move forward with the subject pending registrations. If you need anything further or have other questions, please do not hesitate to call (913-268-2751).

Sincerely,

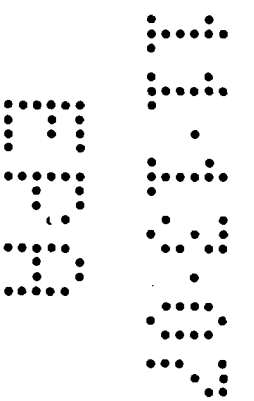
Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs

DAS/FTM

Enclosures:

a) Attachment 1 - "Apoptosis of the External Granular Cell Layer in Neonatal Kittens: Case Summary and Literature Review," 2pp.
b) Attachment 2 - "Histopathological Assessment of Cerebellar Sections," by B.P. Stuart, 2pp.
c) Attachment 3 - Copies of Literature References

CC: Ms. M. Laws - EPA
Mr. K. Davis - EPA



**ATTACHMENT 1: Apoptosis of the External Granular Cell Layer in Neonatal Kittens: Case Summary and Literature Review**

Two companion animal safety studies were performed using Advantage Plus vehicle minus actives applied topically at 5.6x (2 ml) and 5x (1.8 ml) to 8-week-old kittens (MRIDs 47089401 and 47089403, respectively). Following the initial treatments, neurologic signs including mydriasis, tremors, and ataxia followed by death were noted for two kittens from each study. The only microscopic findings of concern described in the pathology report (Rick Long, DVM, DACVP, DABT) were minimal to moderate necrosis with pyknosis and karyorrhexis of the cerebellar external granular layer (EGL) in all four kittens. Although a causal relationship between clinical signs and microscopic findings was not stated in the report, most scientists would presuppose an association between the neurological signs and the cerebellar findings. However, during our recent review of Advantage companion animal safety studies, it was noted that similar histopathological findings were not documented in any other kittens necropsied following treatment with Advantage or Advantage vehicle (MRIDs 44157301 and 4367502). Subsequently, Bayer conducted both a review of the scientific literature and a re-evaluation of available histopathology slides. Our findings, as documented below, demonstrate that the microscopic observations are consistent with a normal physiologic event as opposed to a cerebellar insult.

Both traditional and contemporary literature describes the EGL as a transitory layer of the developing cerebellum. In altricial animals (e.g., humans, rats, puppies, kittens), cells of the EGL are produced in extremely large numbers during the initial postnatal period. These cells then migrate inwards, contributing to the development of the cerebellar cortex.[1, 2, 3, 4] This migration results in the gradual disappearance of the EGL, which is present only for the first few months after birth (specifically 60 to 84 days in kittens).[5] EGL cells which do not migrate die via apoptosis (programmed cell death) which is characterized microscopically by nuclear pyknosis and karyorrhexis,[6, 7, 8] findings identical to those noted by Dr. Long during his evaluation of the four kittens from MRID 47089401 and 47089403.

Histopathology slides of CNS tissues from these four animals (MRID 47089401: #783, 791; and MRID 47089403: #811, 816) were recently presented to Barry Stuart, DVM, PhD, DACVP, for evaluation. Independent of the literature review, Dr. Stuart noted numerous apoptotic cells in the EGL. He also concluded that the surrounding brain tissue, including the molecular, Purkinje, and internal granular layers of the cerebellum, the brain stem, and cerebrum, appeared as normal. Although not discussed in his formal report, Dr. Stuart also reviewed the CNS slides of four kittens necropsied at 7 weeks of age after treatment with 5x Advantage (MRID 44157301; pages 30-37). "No histologic lesions" of the cerebellum were recorded in the initial pathology report (Gordon Andrews, DVM, PhD, DACVP), although apoptotic cells were noted in the EGL by Dr. Stuart, further confirming their presence as a normal developmental finding.

In light of the literature review and re-evaluation of available slides, Bayer concludes that the findings of pyknosis and karyorrhexis in the EGL in four animals from studies MRID

47089401 and 47089403 are indicative of apoptosis and consistent with normal developmental neuroanatomy.

---

**REFERENCES**


[1] Dodgson, M., *The Growing Brain*, Stonebridge Press: Bristol, 1962, p. 65-67.

[2] Kuhlenbeck, H., *The Central Nervous System of Vertebrates*, S. Karger: Basel, 1975, p. 644-648.

[3] McGeady, T., *et al*, *Veterinary Embryology*, Blackwell Publishing Ltd.: Ames, 2006, p. 158-160.

[4] Maxie, M., *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*, 5th Ed., Saunders: Edinburgh, 2007, p 309.

[5] De Lahunta, A., *Veterinary Neuroanatomy and Clinical Neurology*, 2nd Ed., Saunders: Philadelphia, 1983, p. 255-256.

[6] Lossi, L., *et al*, "Apoptosis in the mammalian CNS: Lessons from animal models," *The Veterinary Journal*, 2005, p. 52-66.

[7] Lossi, L., *et al*, "Synapse-Independent and Synapse-Dependent Apoptosis of Cerebellar Granule Cells in Postnatal Rabbits Occur at Two Subsequent but Partly Overlapping Developmental Stages," *Neuroscience*, 2002, p. 509-523.

[8] Zamzami, N., Kroemer, G., "Condensed matter in cell death," *Nature*, Sept 1999, p. 127-128.

**ATTACHMENT 2: Histopathological Assessment of Cerebellar Sections by B. P. Stuart, D.V.M., Ph.D., DACVP (Diplomate of the American College of Veterinary Pathologists)**

On 10-11-07, I evaluated brain tissue presented to me from 8-week-old kittens on which a previous microscopic diagnosis of minimal to moderate necrosis of the cerebellar external granular layer had been reported.

**Evaluation of the General Safety Of 9.1% Imidacloprid With 0.9% Pyriproxyfen Spot-On Formulation in the Target Species Eight-Week-Old Kittens, Study No. 150.851/MRID 47089401**

Both kittens from this study were reported to have demonstrated mydriasis, tremors, and death on Day 1 following the topical treatment with 2 ml (5.6X) vehicle.

Animals #783 and 791

Brain slides (783-1, 783-2, 791-1, and 791-2) had selected regions denoted (circled) which represented paraventricular zones and basilar cortical region (783-1). In the section of cerebellum (slides 783-3 and 791-3), there was a prominent external granular layer characterized by individual cell necrosis (apoptosis) represented by nuclear pyknosis or shrinkage and/or fragmentation. There was no associated inflammatory response. Subtle apoptotic nuclear change was noted in a few cells in the paraventricular zones.

No remarkable histomorphologic changes were observed in the balance of the brain tissue/sections examined.

**Evaluation of the General Safety Of 9.1% Imidacloprid With 0.45% Pyriproxyfen Spot-On With 5.0% Water Blank Formulation in The Target Species, Eight-Week-Old Kittens, Study No. 150.828/MRID 47089403**

Similar brain tissue was also examined from two kittens (#811 and 816). These 8-week-old kittens had been treated topically with 1.8 ml (5X) vehicle. Clinical signs on Day 1 included ataxia, depression, mydriasis, tremors, and death. Necrosis of the cerebellar external granular layers had been previously reported.

Overall, histomorphologic change was similar to that observed in the above study #150.851. Individual cell necrosis (apoptosis) characterized by nuclear pyknosis or fragmentation was present in both kittens (#811 and 816) in the external granular cells of the cerebellum. Kitten #811 had more numerous external granular layer cells than #816, but demonstrated less (grade 1 or minimal) individual cell necrosis than #816 (mild - grade 2 to moderate - grade 3). In addition, there was a subtle presence of apoptotic cells in the paraventricular zones. No inflammatory response was present in the cerebellar (slide 3) or other brain regions examined (slides 1-2) from either kitten.

No remarkable histomorphologic changes were observed in the balance of the brain tissue/sections examined.

**SUMMARY**

In both studies, the nuclear changes in the external granular layer (EGL) of the cerebellar brain sections characterized as pyknosis, fragmentation, or karyorrhexis are compatible with that described in the literature as individual cell necrosis (ICN) or apoptosis. These apoptotic cellular changes are a normal physiologic postnatal developmental event associated with brain development and the migratory functions of the EGL cells. There was no associated inflammatory cell process in either study as previously reported.

B P Stuart

8 Nov 2007
Date

B. P. Stuart, D.V.M., Ph.D., DACVP
Director, Pathology Laboratory
and Veterinary Services
Bayer CropScience LP
17745 S Metcalf
Stilwell, KS 66085

**Doug Spilker**
**<doug.spilker.b@bayer.com>**

09/24/2007 12:18 PM

To Kable Davis/DC/USEPA/US@EPA

cc Venus Eagle/DC/USEPA/US@EPA, Terry McNamara <terry.mcnamara.b@bayer.com>, Ernst Heinen <ernst.heinen.b@bayer.com>

bcc

Subject Advantage Plus 9 (EPA File Symbol 11556-REA) and Advantage Plus 18 (EPA File Symbol 11556-REO)

History: This message has been replied to.

As we discussed in our telephone conversation of September 24, 2007 on the two subject pending actions, Bayer Animal Health requests a 4-month extension of the original PRIA deadline for these two pending registration applications to allow further discussions between Bayer Animal Health and the Agency. We therefore request a re-negotiation of the PRIA due date from the original PRIA due date of September 26, 2007 to a revised date of January 26, 2008.

If you need additional information to support this request, please contact us immediately.

Respectfully,

Douglas A. Spilker

Doug Spilker Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
ANIMAL HEALTH
Office: +1 913-268-2751
Mobile: +1 816-506-3102
Fax: +1 913-268-2135
Email: doug.spilker.b@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Powered by People, Driven by Science"

**Recommendation of Division Directors**
**Negotiated Due Dates**

| | | |
|---|---|---|
| **Decision#:** D-215319; 215319 | **Registration#:** 11556-REA; 11556-REO | **Petition #:** |
| **Fee Category:** R31, R31.1 | **PRIA Decision Time Frame:** | |
| **Submitted by:** Kable Bo Davis | **Branch:** IRB | **Date:** 9/24/07 |
| **Company:** Bayer HealthCare | | |
| **Original Due Date:** 9/26/07 | **Proposed New Due Date:** 1/26/08 | |
| **Previous Negotiated Due Dates:** | | |
| **Is the "Fix" in-house?** Yes | **If not, date "Fix" expected:** | |

**Issue (describe in detail):**

These products were originally submitted for registration in 2000. The companion animal safety study was found acceptable for cats and unacceptable for kittens. In addition, CRP data were required. The registrant withdrew the products.

In March, 2007, Bayer submitted all deficient data. The companion animal safety study was found unacceptable for kittens. The registrant is requesting these products be registered for adult cats only. However, the Technical Review Branch (TRB) has concerns regarding one of the solvents. We are currently waiting for the Information Technology and Resources Management Division (ITRMD) to compile an incident report on two currently registered cat spot on products from Bayer that contain the same solvent of concern and percent a.i. (minus IGR).

**Summary of Deficiency Type(s):** **Not Submitted (N)** **Deficiencies (D)**
**Product Chemistry: ___ Acute Tox: ___ Efficacy: ____ Labeling: ____ Other?: _X_**

**Describe Interactions with Company (describe when contacted and company's response including response to previous negotiated due dates):**
9/10/07- companion animal safety study sent to Bayer (PDF format); Bayer called and asked for meeting
9/17/07- conference call between Agency and Bayer; Bayer said they would withdraw product
9/20/07- Bayer called asking for a renegotiated due date.
9/24/07- Agency received email requesting 4 month extension; new due date: 1-26-08

**"75 Day" Letter sent? _____ (Date sent)Yes** **_X_ No and reason for none?**
The companion animal review was completed less than three weeks before the PRIA due date.

**Rationale for Proposed Due Date:**

We are waiting for an incident report from ITRMD. The number and severity of incidents will help determine if the product can be registered for adult cats.

**Registrant notified that this is the last negotiation? _____Yes __X__Not Applicable**

| | |
|---|---|
| **Approve:** ✓ | **Disapprove:** |

**If disapproved, action to be taken:**

**OD or DOD Signature:** [signature] **Date:** 9-26-07

Revised May 2007

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

6 September 2007

**MEMORANDUM**

| | | |
|---|---|---|
| Subject: | Name of Pesticide Product: | ADVANTAGE PLUS 9 FOR CATS |
| | EPA Reg. No. /File Symbol: | 11556-REA |
| | DP Barcode: | D338710 |
| | Decision No.: | 215319 |
| | PC Codes: | 129099 [Imidacloprid: 9.1%] |
| | | 129032 [Pyriroxyfen: 0.46%] |

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
9/6/2007

To: Kable Davis/Venus Eagle, RM 01
Insecticide-Rodenticide Branch
Registration Division (7505P)

M Hasha
9/6/07

Registrant: BAYER HEALTHCARE LLC

FORMULATION FROM LABEL:

| Active Ingredient(s): | % by wt. |
|---|---|
| 129099 Imidacloprid | 9.1% |
| 129032 Pyriproxyfen | 0.46% |
| Inert Ingredient(s): | 90.44% |
| Total: | 100.00% |

**ACTION REQUESTED:** The Risk Manager requests:

Please review the attached domestic animal safety studies to determine if they support product registration. I have also included copies of the cover letter, amended label and CSF…"

**BACKGROUND:**

The material received for review includes three companion animal (each with 8-week old kittens) studies. One study (MRID 47089401, with additional information in MRID 47089402) involved testing two groups of kittens; one group received 5X of a formulation containing the active ingredients (9.1% Imidacloprid and 0.9% Pyriproxyfen) on Days 0, 7, 14 and 21, while the second group was dosed with ~5.6X the solvents and inerts (no actives) of the proposed formulation on the same days. In the second study (MRID 47089403, with additional information in MRID 47089404) there were again two groups of kittens; one group received 5X applications of the solvents and inerts on Days 0, 7, 14 and 21, while the second group was untreated. In the third study (MRID 47089405, with additional information in MRID 47089406) there were two groups of kittens; one group received 3X applications of the solvents and inerts on Days 0, 7, 14 and 21, while the second group was untreated.

**RECOMMENDATIONS:**

1. Each of the three studies has been classified as supplementary data. An adequate (5X) margin of safety associated with the use exposure to the solvents and/or inerts of this formulation has not been demonstrated. Until it is shown that there is an acceptable 5X margin of safety, these studies cannot be used, by themselves, to support the use of this and/or similar formulations on 8-week-old kittens.

A. In the study MRID 47089401 two of the 14 kittens dosed with ~5.6X the solvents and inerts (no actives) of the proposed formulation had to be euthanized on Day 1. In the study MRID 47089403 two of the 16 kittens dosed with 5X the solvents and inerts (no actives) of the proposed formulation had to be euthanized on Day 1. All four of the euthanized kittens showed clinical signs which included tremors, with incoordination and/or depression and/or dilated pupils and/or rapid breathing. At gross necropsy, each of the four kittens showed a distended urinary bladder. Microscopic examination of all four showed necrosis of cells in the external granular layer of the cerebellum.

B. All four of the kittens which were euthanized in these two studies showed hematology and clinical chemistry findings on Day 1 which included increased neutrophil counts, decreased calcium and phosphorus levels and increases in alkaline phosphatase, aspartate animnotransferase and alanine aminotransferase.

C. Some additional kittens in these first two studies also showed clinical signs (tremors, etc.) of toxicity following an exposure to the test material, but subsequently recovered. Hematology and blood chemistry findings showed some changes similar to (but not as pronounced) as those observed in the euthanized kittens.

2. In the study MRID 47089405 one of the 14 kittens dosed with 3X the solvents and inerts of the proposed formulation showed symptoms (tremors, incoordination) in the period from Day 1 to 3 following application on Day 0. This kitten also had hematology and blood chemistry findings similar to (but not as pronounced) as those observed in the euthanized kittens. The occurrence of these clinical signs of toxicity indicates that the margin of safety associated with exposure to the solvents/inerts of this formulation is less than 3X.

3. No significant indications of toxicity were observed in Group A (exposed to the formulation with active ingredients) kittens of the study in MRID 47089401. One possible explanation for the greater severity of symptoms in kittens exposed to the solvents/inerts was that the observed toxicity was due to oral ingestion of the solvent(s), but that a bad taste or some other unpleasant sensation association with the active ingredients resulted in considerable less oral ingestion by kittens that were exposed to the formulation with actives.

4. TRB is aware that the percentages of solvents and inerts of this proposed formulation are similar to those of several existing imidacloprid-containing products which are registered for use on kittens of 8 weeks of age and older. A check of our records indicates the supporting kitten study (dated August 30, 1996, in MRID 44157302) for a representative product was reviewed and accepted by HED 9/17/97, but that the study used two groups, one of which was treated with the 9.1% imidacloprid at 5X (2.0 mL) the recommended use rate of 0.4 mL at weekly intervals for 8 treatments, while the second was treated with the vehicle control at the recommended use (exposure) rate of 0.4 mL at weekly intervals for 8 treatments. This study was conducted prior to the publication (August, 1998) of the 870.7200 companion animal safety study guidelines which state that: "The vehicle control should be administered at a 5X level. The vehicle should contain the inert ingredients at the maximum levels that would appear in the 5X formulation."

5. The studies (MRIDs 47089401 through 47089406) have laboratory dates of 2000-2001, but have only been recently submitted to the Agency. Since these studies demonstrate potential adverse [6(a)(2)] effects associated with exposure to the solvent(s)/inerts in this formulation, they should have been submitted to the Agency as soon as the findings became known.

**EPA Primary Reviewer: Byron T. Backus, Ph.D.**
**Technical Review Branch, Registration Division (7505P)**
**EPA Secondary Reviewer: Masih Hashim, D.V.M., Ph.D.**
**Technical Review Branch, Registration Division (7505P)**

**Signature:** Byron T. Backus
**Date:** 9/6/2007
**Signature:** M. Hashim
**Date:** 9/6/07

**DATA EVALUATION RECORD**

**STUDY TYPE: Companion Animal Safety - Kittens (OPPTS 870.7200)**

**PC CODES: 129099 (Imidacloprid); 129032 (Pyriproxyfen)**

**DP BARCODE: D338710**

**DECISION NO.: 215319**

**RISK MANAGER: (EPA): 01**

**TEST MATERIAL AND PRODUCT:** Imidacloprid (9.1%) and Pyriproxyfen (0.9%) in the final formulation. After examinining page 2 of the Confidential Appendices in MRID 47089401 and comparing the information with that in the CSF (dated March 8, 2007) for 11556-REA (Advantage® Plus 9 for Cats, with 9.1% Imidacloprid and 0.46% Pyriproxyfen) it is concluded that studies conducted on the test formulation could be used to support the registration of 11556-REA provided they demonstrate an adequate margin of safety.

**CITATION:** Abraham, A. S. (2001). Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-on Formulation in the Target Species, 8-Week Old Kittens. Performing Laboratory: Intervet Inc. (formerly a facility owned and operated by Bayer Corporation Agriculture Division Animal Health), DeSoto Research Facility, DeSoto, Kansas 66018. Laboratory Project ID 75120 (150.851). Study Dated June 8, 2001. MRID 47089401. 160 p. + a 2 p. confidential appendix.

**SPONSOR:** Bayer Corporation Agriculture Division

**SUBMITTER:** Bayer HealthCare LLC, Animal Health Division, P.O. Box 390, Shawnee, KS 66201

**EXECUTIVE SUMMARY:** In a companion animal safety study (MRID 47089401), there were two groups, each containing 7 male and 7 female kittens (from 7 weeks 5 days to 8 weeks old; day -1 bodyweights: males: 1.14-2.09 lbs; females: 1.42-2.10 lbs; source: Harlan Sprague Dawley, Inc., Madison, WI). Kittens in Group A were treated with the formulation containing actives (Imidacloprid: 9.1%; Pyriproxyfen: 0.9%) at 5X the label-specified use application rate of 0.4 mL (5 x 0.4 mL = 2.0 mL) while kittens in Group B were treated with 2.0 mL of vehicle (solvent) material (equal to ~5.6X the amount of solvents and non-active ingredients from a single use application of the proposed product). The dose was applied topically on the backside of the head and the neck of each kitten to avoid runoff. Kittens were treated on Days 0, 7, 14 and 21; the proposed label indicates once-a-month treatment, so that each of the kittens in Group A received a cumulative total of 20X of the proposed monthly dosage of the formulation while kittens in Group B received a cumulative total of ~22.4X of the proposed monthly dosage of solvents and non-active ingredients. At the end of the study the heaviest kitten was 3.93 lbs, so none reached a weight >9 lbs (4.1 kg) which would have resulted in an increase in the 1X dose from 0.4 to 0.8 mL.

On the days of dosing (Days 0, 7, 14 and 21) each kitten was observed five times, once prior to dosage and then at hourly intervals for four hours after application. Otherwise, clinical observations were made twice a day. Individual daily food consumption was determined visually, using a scoring

system (≥75% consumption = 1, 25-75% consumption = 2, ≤25% consumption = 3). The kittens were weighed at six times before and during the study (Days -14, -7, -1, 13, 28 and 38). Blood samples were taken on Days -7, -1, 1, 22, and 38. Blood samples from four kittens were also collected on study day 2, from 3 kittens on study days 22-23 (insufficient initial samples and machine malfunction) and blood was collected a second time from one kitten on day 38 (due to clotting). Prothrombin time and activated partial thromboplastic time measurements were not done because of the comparatively large amount of blood required for these tests and the age of the kittens; this protocol deviation had been previously discussed with and accepted by the Agency.

Signs of toxicity in Group A (formulation with active ingredients) kittens following the Day 0 treatment were salivation (2 females) and salivation accompanied by sneezing (one male). One of the two affected females had nasal discharge on Day 1. Following treatment on Day 7 one male (#792) showed depression, rapid respiration and vomiting; however, this male had also shown these signs shortly before dosage. Male #792 subsequently showed rapid respiration, slowness of movement and unsteadiness on Day 8, and received 24 mL Lactated Ringers Solution (LRS) + 2 mg Ceftiofur + 0.5 mg Re-Covr. Following the Day 7 treatment another male (#775) was slow to move and depressed, and also had diarrhea on Days 8 and/or 9. On Day 9 #775 was treated with 24 mL LRS + 2 mg Ceftiofur + 0.5 mg Re-Covr, also 2 mg Ceftiofur on Day 10. It is stated that symptoms in #775 were not due to test material and may have been from bacterial enteritis. During the observation period following the Day 14 treatment 2 females showed pruritis.

Two male kittens (same sire, but from different mothers) in Group B had adverse reactions to the solvent control (vehicle) and died on Day 1. Signs observed prior to death in one of the kittens were sneezing, salivation, dilated pupils, rapid breathing, generalized tremors and slow movement. Signs in the other kitten were dilated pupils, rapid breathing and generalized tremors. In the blood samples taken on day 1 both of these male kittens showed a number of physiologically significant hematology and blood chemistry changes, including increases in neutrophils, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), and decreases in potassium (K), phosphorus (P) and calcium (Ca). At gross necropsy both had distended urinary bladders. On microscopic examination, both showed necrosis in the external granular layer of the cerebellum and lymphoid tissues. Other necropsy findings were incidental and/or considered to be secondary to the moribund condition of the kittens.

There were no signs of toxicity in other Group B kittens following the Day 0 treatment. Following the Day 7 treatment one Group B male had a number of signs which included tremors, slowness of movement, vomiting and dilated pupils on Days 8-9. The same male also had sneezing following the application on Day 14, followed by depression, tremors, disorientation and dilated pupils on Days 16-18. This male (#776) had a different sire from that of the two kittens which died. One female showed pruritis in the observation period following the Day 14 treatment.

One female (#788) in Group B had tremors on days 22 and 23 and dilated pupils, unsteadiness and apprehensiveness on day 23, and also had noticeably reduced potassium, phosphorus and calcium levels on Day 22. In addition, female solvent control kitten #797 (not reported as having any signs of toxicity) had slightly reduced potassium and somewhat elevated ASP and ALT on Day 22. Values were within normal ranges for both of these kittens on Day 38. One possible explanation for the greater severity of symptoms seen in the Group B (solvent control) kittens was that the toxicity was a result of oral ingestion of the solvent(s), but that a bad taste or some other unpleasant sensation associated with the active ingredients resulted in considerably less oral ingestion of the test material in the Group A kittens.

This study is classified as **Supplementary** as a companion animal safety study (OPPTS 870.7200), as it does not demonstrate a 5X margin of safety associated with exposure to the solvents/inerts and the proposed use of the formulation (with actives) in 8 week old kittens.

**COMPLIANCE:** Signed and dated Quality Assurance (p. 4), [No] Data Confidentiality (p. 2) and Good Laboratory Practice Compliance (p. 3) statements are present.

## I. MATERIAL

MATERIALS

1. Test material: 9.1% Imidacloprid with 0.9% Pyriproxyfen (w/w) spot-on formulation.
   Description: A liquid with a specific gravity of (see p. 156 of MRID 47089401) 1.097 g/mL.
   Lot No.: 99-901-66.
   Storage: Stored in amber glass bottles at room temperature.
   Placebo: The test material without the two active ingredients.
   Description: A liquid with a specific gravity of (from p. 157 of MRID 47089401) 1.0674 g/mL.
   Lot No.: 99-901-68
   Storage: Stored in amber glass bottles at room temperature (15° -30°C)

2. Administration: Topically applied to the backside of the head and the neck of each kitten to avoid run off.
3. Test animals
   Species: Cat
   Breed: Domestic Short hair
   Ages and weights at study initiation (Day 0, day of dosing): Males: 7 weeks 5 days to 8 weeks; 1.14 to 2.09 lbs; Females: 7 weeks 6 days to 8 weeks; 1.42 to 2.10 lbs. [Note: weights for both sexes are for Day -1].
   Source: Harlan Sprague Dawley, Inc., Madison, WI 53744
   Vaccinations: The kittens had been vaccinated with a four way feline vaccine, Fel-O-Vax IV (Feline Rhinotracheitis, Calici, Panleukopenia, Chlamydia Psittaci Vaccine) prior to acclimation.
   Housing: individual in cages with at least 3 $ft^2$ of floor space and at least 24 inches high.
   Diet: Harlan Teklad® (commercial dry cat feed) and a canned kitten food (Feline Growth) from Hill's Pet Nutrition, Kansas City, MO. (fed once daily, however, no information is provided as to the amount that was offered).
   Water: Tap water, *ad libitum*
   Environmental conditions:
      Temperature: (not stated)
      Humidity: (not stated)
      Air changes: (not stated)
      Photoperiod: 9-14 hours of lighting/day
   Acclimation period: 14 days

## II. STUDY DESIGN

A. IN LIFE DATES

From the report (p. 12 of MRID 47089401): Day 0 was September 21, 1999. The experimental phase of the study was completed on February 28, 2000 (histopathology slides read).

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

From p. 14 of MRID 47089401: "Twenty-eight animals were randomly allocated to two groups. Animals were blocked by sex and ranked by ascending order of study day -1 body weight and assigned a random number. From the first block (female), the animal with the larger of the first two random numbers was assigned to Group A (test substance), and the smaller to Group B (placebo) and so forth until all the animals of the same sex were assigned. This procedure was repeated for the males..."

From p. 19 of MRID 47089401: "Seven males and seven females in group A were dosed weekly for four weeks with 5 times the monthly use rate volume (2 mL [5 x 0.4 mL dosage rate for kittens weighing less than 9 lbs]...) of test substance. This resulted in a 20X the monthly use volume applied during a month's time."

"Seven male and seven females in group B were dosed with 5 times the monthly use rate volume (2 mL for kittens up to 9 lbs of body weight) of placebo without either of the active ingredients. This treatment resulted in 5.6X the vehicle content, as the test article was 10% by weight (11% by volume) of active ingredients and 0.2 mL of active ingredients. Thus, by giving the kitten a full 2 mL of vehicle (instead of 1.8 mL of vehicle), the kitten received a 5.6X overdose of vehicle. This resulted in a 22.4X the monthly use volume applied in a month's time."

From p. 20 of MRID 47089401: "The dose was administered topically on the backside of the head and the neck of each kitten to avoid run off of the test or control substance... The kittens were dosed four times: on study days 0, 7, 14, and 21."

**TABLE 1. Study design**

| Group & Weight Range (lb) | | Number of kittens | Mean Kitten Weight: Mean Kitten Wt ± S.D. (lb) on Day -1 (before 1st application) | Mean Kitten Wt ± S.D. (lb) on Day 13 (before 3rd application) | Mean Kitten Wt ± S.D. (lb) on Study Day 28 | Mean Kitten Wt ± S.D. (lb) on Study Day 38 |
|---|---|---|---|---|---|---|
| Con-trol (B) | males ≤ 9 lb | 7* | 1.62 ± 0.28 | 2.18 ± 0.31 | 3.01 ± 0.36 | 3.36 ± 0.35 |
| | females ≤ 9 lb | 7 | 1.73 ± 0.21 | 2.26 ± 0.19 | 2.90 ± 0.21 | 3.25 ± 0.26 |
| | combined ≤ 9 lb | 14** | 1.67 ± 0.24 | 2.23 ± 0.24 | 2.94 ± 0.27 | 3.29 ± 0.29 |
| 5X (A) | males ≤ 9 lb | 7 | 1.60 ± 0.30 | 2.06 ± 0.18 | 2.98 ± 0.32 | 3.36 ± 0.31 |
| | females ≤ 9 lb | 7 | 1.75 ± 0.17 | 2.24 ± 0.22 | 3.04 ± 0.32 | 3.36 ± 0.33 |
| | combined ≤ 9 lb | 14 | 1.68 ± 0.25 | 2.15 ± 0.22 | 3.01 ± 0.31 | 3.36 ± 0.31 |

Data calculated from information on p. 42 of MRID 47089401.
*5 kittens on Days 13, 28 and 38, as two kittens had died on Day 1.
**12 kittens on Days 13, 28 and 38, as two kittens had died on Day 1.

C. DOSE SELECTION RATIONALE

From p. 11 of MRID 47089401: "The study was conducted to evaluate the safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen (w/w) spot-on formulation or vehicle in 8-week old kittens applied at 5 and 5.6X times the use volume rate, respectively, at one week intervals for a total of 4 weeks. This study was designed as a limit test, and a full study

with three dose levels 1X, 3X and 5X was not conducted. This study supports the registration of other similar formulations."

D. EXPERIMENTAL DESIGN

There were two groups, each containing 7 male and 7 female kittens (from 7 weeks 5 days to 8 weeks old; day -1 bodyweights: males: 1.14-2.09 lbs; females: 1.42-2.10 lbs). Kittens in Group A were treated with the proposed product at 5X the label-specified use application rate of 0.4 mL (5 x 0.4 mL = 2.0 mL) while kittens in Group B were treated with 2.0 mL of vehicle (equal to ~5.6X the amount of solvents and non-active ingredients from a single use application of the proposed product). The dose was applied topically on the backside of the head and the neck of each kitten to avoid runoff. The dose was administered by parting the hair and using a syringe without a needle. Kittens were treated on Days 0, 7, 14 and 21; since the proposed label indicates once-a-month treatment, each of the kittens in Group A received a cumulative total of 20X of the proposed monthly dosage of the formulation while kittens in Group B received a cumulative total of ~22.4X of the proposed monthly dosage of solvents and non-active ingredients. At the end of the study the heaviest kitten was 3.93 lbs, so none had reached a weight >9 lbs (4.1 kg) which would have resulted in an increase in the 5X dose from 2.0 to 4.0 mL.

On the days of dosing (Days 0, 7, 14 and 21) each kitten was observed five times, once prior to dosage and then at hourly intervals for four hours after application. Otherwise, clinical observations were made twice (once in the a.m., once in the p.m.) a day. Individual daily food consumption was determined visually, using a scoring system ($\geq$75% consumption = 1, 25-75% consumption = 2, $\leq$25% consumption = 3). The kittens were weighed at six times before and during the study (Days -14, -7, -1, 13, 28 and 38). Blood samples were taken on Days -7, -1, 1, 22, and 38. Blood samples from four kittens were also collected on study day 2, from 3 kittens on study days 22-23 (insufficient initial samples and machine malfunction) and blood was collected a second time from one kitten on day 38 (due to clotting). Prothrombin time and activated partial thromboplastic time measurements were not done because of the comparatively large amount of blood required for these tests and the age of the kittens; this protocol deviation had been previously discussed with and accepted by the Agency.

"Physical examinations were performed on the kittens on study day -14, on study day -1, and on study day 35."

E. CLINICAL PATHOLOGY PARAMETERS

Blood samples were collected from each kitten on study Days -7, -1, 1, 22 and 38. There is no indication within the report of fasting prior to collection of blood. The CHECKED (X) parameters were examined:

a. Hematology

| | | | |
|---|---|---|---|
| X | | X | |
| X | Hematocrit (HCT)* | X | Leukocyte differential count* |
| X | Hemoglobin (HGB)* | X | Absolute and percent basophil count |
| | | X | Absolute and percent eosinophil count |
| X | Leukocyte count (WBC)* | X | Absolute and percent lymphocyte count |
| X | Erythrocyte count (RBC)* | X | Absolute and percent monocyte count |
| | | X | Absolute and percent neutrophil count |
| X | Platelet count (PLTS) | X | Mean corpuscular HGB (MCH)* |
| | Blood clotting measurements | X | Mean corpusc. HGB conc.(MCHC)* |
| | (Thromboplastin time) | X | Mean corpusc. volume (MCV)* |
| | (Clotting time) | | |
| | (Prothrombin time [PT])* | | |
| | (Activated partial thromboplastin time [APTT])* | | |

*Recommended in OPPTS 870.7200 Guidelines. The Prothrombin time and Activated partial thromoplastin time were not done because of the comparatively large volume of blood required for these tests and the age of the kittens. This deviation had been accepted by the Agency prior to initiation of this study.

b. Clinical chemistry

| X | ELECTROLYTES | X | OTHER |
|---|---|---|---|
| X | Calcium* | X | Albumin (Alb)* |
| X | Chloride* | X | Creatinine (Crea)* |
| | Magnesium | X | Blood urea nitrogen (BUN)* |
| X | Phosphorus* | | Total Cholesterol |
| X | Potassium* | X | Globulin (Glob)* |
| X | Sodium* | X | Glucose (Gluc)* |
| | | X | Total bilirubin (T Bil)* |
| | ENZYMES | X | Direct bilirubin (D Bil)* |
| | | | Total protein (TP)* |
| X | Alkaline phosphatase(ALP or ALK)* | | Triglycerides |
| | Cholinesterase(ChE) | | Serum protein electrophoresis |
| | Creatine phosphokinase | X | Albumin/Globulin (A/G) ratio |
| | Lactic acid dehydrogenase(LDH) | | Lipase |
| X | Serum alanine aminotransferase (ALT or SGPT)* | | |
| X | Serum aspartate aminotransferase(AST or SGOT)* | X | BUN/Creatinine ratio |
| | | X | Ca/Phos Ratio |
| | Gamma glutamyl transpeptidase(GGT) | X | Na/K Ratio |
| | Amylase | | |

*Recommended in OPPTS 870.7200 Guidelines.

F. CONCOMITANT MEDICATIONS

From p. 20 of MRID 47089401: "On study day -4, coccidiosis was diagnosed in the kittens. Starting on study day -4 through study day -1, the kittens were treated once daily orally with Sulfamethoxisol/Trimethoprim liquid at approximately 15 mg and 3 mg/pound body weight, respectively. Then from study day 3 through study day 9 the kittens were treated once daily orally with Albon Suspension (Sulfadimethoxine). On the first day of dosing (study day 3) the animals received approximately 25 mg of Sulfadimethoxine per pound of body weight. On subsequent days (study days 4 to 9) the animals received approximately 12.5 mg of Sulfadimethoxine per pound of body weight."

G. STATISTICS

Although means and standard deviations were calculated for some parameters (such as body weight), statistical tests were primarily applied to chemistry and hematology pathology parameters. From p. 132 of MRID 47089401: "This study is intended to confirm the general safety of the test substance and approximately the same number of adverse effects is expected between the two groups. Adverse effects will be summarized in tables. Certain types of adverse effects may be grouped together, depending on the clinical presentation, such as all effects, all transient effects or all blood chemistry effects. If the number or pattern of effects elicit clinical interest, incidence rates will also be compared between groups." For the clinical pathology parameters, it is stated (p. 22 of MRID 47089401): "For each animal and for each clinical pathology test, a baseline value was calculated by averaging the two pretreatment measurements (study days -7 and -1). Each clinical pathology test was then analyzed with a multivariate repeated measures ANOVA (baseline, study days 1, 22, and 38) including terms for Group, Sex, Animal (random), Day, and Group*Day as the predictors..."

H. DISPOSITION OF ANIMALS

From p. 14 of MRID 47089401: "One animal not included in the experimental phase of the study was euthanized due to poor health on September 21, 1999. Two animals [on test] died on study day 1. Twenty-five animals in the experimental phase of the study were euthanized on November 01, 1999. One animal in the experimental phase of the study and one animal not in the experimental phase of the study were given for adoption as pets." According to the OPPTS 870.7200 Guidelines: "Routine sacrifice or necropsy is not required for surviving animals."

I. COMPLIANCE

Signed and dated Quality Assurance [p. 4], [No] Data Confidentiality [p. 2], and Good Laboratory Practice (GLP) Compliance [p. 3] Statements were present.

## III. RESULTS

A. EXPOSURE LEVELS

Refer to Table 1 of this DER. Kittens in the control group (Group B), all weighing $\leq$ 9.0 lb, were dosed with 2.0 mL of the test material formulation without active ingredients at

each application, while kittens in the test group (Group A), also all weighing ≤ 9.0 kg, were dosed with 2.0 mL of the complete formulation at each application. Applications were made on Days 0, 7, 14 and 21.

B. MORTALITY

Two control (Group B) male kittens died on Day 1; all other kittens survived the 38-day observation period.

C. CLINICAL SIGNS

Group A (test material treated): Signs of toxicity following the Day 0 treatment were salivation (2 females) and salivation accompanied by sneezing (one male). One of the two affected females had nasal discharge on Day 1. Following the Day 7 treatment one male was slow to move and depressed on Days 8-9. Another male showed rapid respiration, depression and vomiting in the 4-hour observation period following treatment, as well as unsteadiness on day 8; however, this male had shown vomiting, depression and rapid respiration immediately before dosage. Following the Day 14 treatment 2 females showed pruritis in the 4-hour observation period after dosage.

Two male kittens (same sire, but from different mothers) in Group B had adverse reactions to the control substance and died on Day 1. One of the kittens had shown sneezing and salivation in the four hour period after treatment. Both kittens showed rapid breathing, dilated pupils, and tremors on day 1 prior to death.

There were no signs of toxicity in other Group B (control) kittens following the Day 0 treatment. Following the Day 7 treatment one Group B male had a number of signs which included tremors, slowness of movement, vomiting and dilated pupils on Days 8-9. The same male also had sneezing following the application on Day 14, followed by depression, tremors, disorientation and dilated pupils on Days 16-18. This male (#776) had a different sire from that of the two kittens which died. One female showed pruritis in the observation period following the Day 14 treatment.

**TABLE 2a. Observed Signs of Toxicity After First Application (Day 0)**

| Group | Signs in the 4-hour observation period | Signs in the two days following treatment |
|---|---|---|
| **Control (B)** | Sneezing, salivation in male #783. | Rapid respiration, dilated pupils, tremors & death in 2 males (#783 & #791) on day 1. Kitten #783 received 12 mL Lactated Ringers Solution subcutaneously on day 1. |
| **5X Test Material (A)** | Sneezing in 2 females (#773, #777); salivation & sneezing in one male (#775) | Nasal discharge in one female (#777). |

Data from information on p. 38 of MRID 47089401.

| TABLE 2b. Observed Signs of Toxicity After Second Application (Day 7) | | |
|---|---|---|
| **Group** | **Signs in the 4-hour observation period** | **Signs in the two days following treatment** |
| **Control (B)** | None reported. | Male #776 had tremors, slowness of movement, vomiting & unsteadiness on days 8 and/or 9. Male #801 vomited on day 8. |
| **5X Test Material (A)** | One male (#792) showed depression, rapid respiration and vomiting; however, this male had also shown these signs shortly before dosage. | Male #792 showed rapid respiration, slowness of movement and unsteadiness on day 8. This kitten received 24 mL of Lactated Ringers solution + 2 mg Ceftiofur + 0.5 mg Re-Covr subcutaneously. Another male (#775) showed slowness of movement, apprehensiveness, diarrhea and depression on days 8 and/or 9. On study day 9 #775 received 24 mL Lactated Ringers Solution, 2 mg Ceftiofur + 0.5 mg Re-Covr subcutaneously; also 2 mg Ceftiofur on study day 10. It is stated that symptoms for #775 may have been due to bacterial enteritis. |

Data from information on p. 38 of MRID 47089401.

| TABLE 2c. Observed Signs of Toxicity After Third Application (Day 14) | | |
|---|---|---|
| **Group** | **Signs in the 4-hour observation period** | **Signs in the two days following treatment** |
| **Control (B)** | One male (#776) showed sneezing; one female (#800) showed pruritus. | One male (#776) showed depression, tremors and disorientation on days 15 and/or 16, and had dilated pupils on days 16 and 17. |
| **5X Test Material (A)** | Two females (#773, #794) showed pruritus. | None reported. |

Data from information on p. 39 of MRID 47089401.

| TABLE 2d. Observed Signs of Toxicity After Fourth Application (Day 21) | | |
|---|---|---|
| **Group** | **Signs in the 4-hour observation period** | **Signs in the two days following treatment** |
| **Control (B)** | None reported. | One female (#788) showed tremors on days 22 and 23; had dilated pupils, unsteadiness and was apprehensive on day 23. |
| **5X Test Material (A)** | None reported. | None reported. |

Data from information on p. 39 of MRID 47089401.

D. NEUROLOGICAL OBSERVATIONS

Some of the effects (tremors, disorientation, dilated pupils) observed in Group B kittens were consistent with neurotoxicity

E. BODY WEIGHT AND WEIGHT GAIN

All surviving kittens (in both the control and test material groups) had good weight gains from day -1 to 13, from day 13 to 28, and again from day 28 to 38. Two of the kittens, male #782 (assigned to the test material group) and male #791 (assigned to the control or solvent group) had slight weight losses pre-exposure. Male #782 went from 1.23 lbs on study day -7 to 1.14 lbs on study day -1, while #791 went from 1.06 lbs on study day -14 to 1.05 lbs on study day -7.

F. FOOD CONSUMPTION

No information is provided as to the exact (or even approximate) amount of food that was offered to kittens on a daily basis. As agreed with EPA, the amount of food consumed was determined visually, with 1 representing $\geq$ 75% offered food consumed, 2 being 25-75% consumption, and 3 representing <25% consumption. Most of the food consumption values were "1." The only values of "3" in Group A (test material treated kittens) after Day 0 were with male #792 on days 7 and 8 (coinciding with depression, rapid respiration and vomiting; signs observed prior to dosing on Day 7), and in male #775 on Day 9. For Group B there were two sporadic occurrences of "3" (male #776 on Day 9, correlating with other effects noted on Days 8-9; and female #793 on Day 24).

G. HEMATOLOGY

There were no physiologically significant changes or variations in hematology values.

H. CLINICAL CHEMISTRY

In the two male solvent control kittens (#783 and #791) which died on Day 1, there were a number of physiologically significant blood chemistry changes, including increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline

phosphatase (ALP), and decreases in potassium (K), phosphorus (P) and calcium (Ca).

**TABLE 3. Blood Chemistry Changes in Kittens Dying on Day 1**

| Kitten + Parameter | Day -7 Value | Day -1 Value | Day 1 Value |
|---|---|---|---|
| **#783:** | | | |
| **Neutrophils** | 5.40 x $10^3$/µL | 11.71 x $10^3$/µL | **34.67** x $10^3$/µL |
| **Potassium (K)** | 5.10 mmol/L | 5.60 mmol/L | **3.30** mmol/L |
| **Phosphorus (P)** | 8.30 mg/dL | 7.80 mg/dL | **4.40** mg/dL |
| **Calcium (Ca)** | 11.00 mg/dL | 11.00 mg/dL | **5.90** mg/dL |
| **ALP** | 213 u/L | 231 u/L | **371** u/L |
| **AST** | 22 u/L | 22 u/L | **161** u/L |
| **ALT** | 53 u/L | 66 u/L | **396** u/L |
| **#791:** | | | |
| **Neutrophils** | 4.62 x $10^3$/µL | 7.00 x $10^3$/µL | **40.43** x $10^3$/µL |
| **Potassium (K)** | 4.50 mmol/L | 6.20 mmol/L | **3.60** mmol/L |
| **Phosphorus (P)** | 7.10 mg/dL | 8.40 mg/dL | **4.90** mg/dL |
| **Calcium (Ca)** | 10.60 mg/dL | 10.80 mg/dL | **6.90** mg/dL |
| **ALP** | 91 u/L | 86 u/L | **437** u/L |
| **AST** | 27 u/L | 34 u/L | **251** u/L |
| **ALT** | 29 u/L | 25 u/L | **51** u/L |

Data from information on p. 71 & 78 of MRID 47089401.

Female solvent control kitten (#788) with tremors on days 22 and 23 and dilated pupils, unsteadiness and apprehensiveness on day 23 had noticeably reduced potassium, phosphorus and calcium levels on Day 22. In addition, female solvent control kitten #797 (no signs of toxicity) had slightly reduced potassium and somewhat elevated AST and ALT on Day 22. Values were within normal ranges for both kittens on Day 38.

**TABLE 4. Blood Chemistry Values in #788 & #797**

| Kitten + Parameter | Day -7 | Day -1 | Day 1 | Day 22 | Day 38 |
|---|---|---|---|---|---|
| **#788:** | | | | | |
| **Neutrophils** | 7.35 x $10^3$/µL | 7.69 x $10^3$/µL | 12.23x$10^3$/µL | **16.83**x$10^3$/µL | 7.22 x $10^3$/µL |
| **Potassium (K)** | 7.10 mmol/L | 6.50 mmol/L | 6.30 mmol/L | **3.90** mmol/L | 4.90 mmol/L |
| **Phosphorus (P)** | 9.30 mg/dL | 8.60 mg/dL | 9.00 mg/dL | **6.70** mg/dL | 7.20 mg/dL |
| **Calcium (Ca)** | 11.00 mg/dL | 10.80 mg/dL | 11.20 mg/dL | **8.00** mg/dL | 10.60 mg/dL |
| **ALP** | 53 u/L | 113 u/L | 119 u/L | 134 u/L | 102 u/L |
| **AST** | 52 u/L | 31 u/L | 33 u/L | 38 u/L | 17 u/L |
| **ALT** | 76 u/L | 57 u/L | 62 u/L | 76 u/L | 60 u/L |
| **#797:** | | | | | |
| **Neutrophils** | 6.42 x $10^3$/µL | 12.67x$10^3$/µL | 14.19x$10^3$/µL | 10.11x$10^3$/µL | 27.26x$10^3$/µL |
| **Potassium (K)** | 6.80 mmol/L | 5.40 mmol/L | 4.90 mmol/L | **3.80** mmol/L | 4.90 mmol/L |
| **Phosphorus (P)** | 9.10 mg/dL | 8.80 mg/dL | 8.00 mg/dL | 8.10 mg/dL | 7.90 mg/dL |
| **Calcium (Ca)** | 10.20 mg/dL | 10.80 mg/dL | 10.80 mg/dL | 10.60 mg/dL | 10.30 mg/dL |
| **ALP** | 137 u/L | 167 u/L | 183 u/L | 151 u/L | 159 u/L |
| **AST** | 33 u/L | 19 u/L | 24 u/L | **48** u/L | 24 u/L |
| **ALT** | 91 u/L | 46 u/L | 50 u/L | **108** u/L | 57 u/L |

Data from information on p. 76 & 83 of MRID 47089401.

I. NECROPSY FINDINGS

At gross necropsy both of the two male kittens of the control group which died on Day 1 had distended urinary bladders. On microscopic examination, both showed necrosis in the external granular layer of the cerebellum and lymphoid tissues. Other findings were incidental and/or considered to be secondary to the moribund condition of the kittens.

## IV. DISCUSSION

In a companion animal safety study (MRID 47089401), there were two groups, each containing 7 male and 7 female kittens (from 7 weeks 5 days to 8 weeks old; day -1 bodyweights: males: 1.14-2.09 lbs; females: 1.42-2.10 lbs; source: Harlan Sprague Dawley, Inc., Madison, WI). Kittens in Group A were treated with the formulation containing actives (Imidacloprid: 9.1%; Pyriproxyfen: 0.9%) at 5X the label-specified use application rate of 0.4 mL (5 x 0.4 mL = 2.0 mL) while kittens in Group B were treated with 2.0 mL of vehicle (equal to ~5.6X the amount of solvents and non-active ingredients from a single use application of the proposed product). The dose was applied topically on the backside of the head and the neck of each kitten to avoid runoff. Kittens were treated on Days 0, 7, 14 and 21; the proposed label indicates once-a-month treatment, so that each of the kittens in Group A received a cumulative total of 20X of the proposed monthly dosage of the formulation while kittens in Group B received a cumulative total of ~22.4X of the proposed monthly dosage of solvents and non-active ingredients. At the end of the study the heaviest kitten was 3.93 lbs, so none reached a weight >9 lbs (4.1 kg) which would have resulted in an increase in the 1X dose from 0.4 to 0.8 mL.

On the days of dosing (Days 0, 7, 14 and 21) each kitten was observed five times, once prior to dosage and then at hourly intervals for four hours after application. Otherwise, clinical observations were made twice a day. Individual daily food consumption was determined visually, using a scoring system ($\geq$75% consumption = 1, 25-75% consumption = 2, $\leq$25% consumption = 3). The kittens were weighed at six times before and during the study (Days -14, -7, -1, 13, 28 and 38). Blood samples were taken on Days -7, -1, 1, 22, and 38. Blood samples from four kittens were also collected on study day 2, from 3 kittens on study days 22-23 (insufficient initial samples and machine malfunction) and blood was collected a second time from one kitten on day 38 (due to clotting). Prothrombin time and activated partial thromboplastic time measurements were not done because of the comparatively large amount of blood required for these tests and the age of the kittens; this protocol deviation had been previously discussed with and accepted by the Agency.

Signs of toxicity in Group A kittens following the Day 0 treatment were salivation (2 females) and salivation accompanied by sneezing (one male). One of the two affected females had nasal discharge on Day 1. Following treatment on Day 7 one male (#792) showed depression, rapid respiration and vomiting; however, this male had also shown these signs shortly before dosage. Male #792 subsequently showed rapid respiration, slowness of movement and unsteadiness on Day 8, and received 24 mL Lactated Ringers Solution (LRS) + 2 mg Ceftiofur + 0.5 mg Re-Covr. Following the Day 7 treatment another male (#775) was slow to move and depressed, and also had diarrhea on Days 8 and/or 9. On Day 9 #775 was treated with 24 mL LRS + 2 mg Ceftiofur + 0.5 mg Re-Covr, also 2 mg Ceftiofur on Day 10. It is stated that symptoms in #775 were not due to test material and may have been from bacterial enteritis. During the observation period following the Day 14 treatment 2 females showed pruritis.

Two male kittens (same sire, but from different mothers) in Group B had adverse reactions to the solvent control (vehicle) and died on Day 1. Signs observed prior to death in one of the kittens were sneezing, salivation, dilated pupils, rapid breathing, generalized tremors

and slow movement. Signs in the other kitten were dilated pupils, rapid breathing and generalized tremors. In the blood samples taken on day 1 both of these male kittens showed a number of physiologically significant hematology and blood chemistry changes, including increases in neutrophils, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), and decreases in potassium (K), phosphorus (P) and calcium (Ca). At gross necropsy both had distended urinary bladders. On microscopic examination, both showed necrosis in the external granular layer of the cerebellum and lymphoid tissues. Other necropsy findings were incidental and/or considered to be secondary to the moribund condition of the kittens.

There were no signs of toxicity in other Group B kittens following the Day 0 treatment. Following the Day 7 treatment one Group B male had a number of signs which included tremors, slowness of movement, vomiting and dilated pupils on Days 8-9. The same male also had sneezing following the application on Day 14, followed by depression, tremors, disorientation and dilated pupils on Days 16-18. This male (#776) had a different sire from that of the two kittens which died. One female showed pruritis in the observation period following the Day 14 treatment.

One female (#788) in Group B had tremors on days 22 and 23 and dilated pupils, unsteadiness and apprehensiveness on day 23, and also had noticeably reduced potassium, phosphorus and calcium levels on Day 22. In addition, female solvent control kitten #797 (not reported as having any signs of toxicity) had slightly reduced potassium and somewhat elevated ASP and ALT on Day 22. Values were within normal ranges for both of these kittens on Day 38. One possible explanation for the greater severity of symptoms seen in the Group B (solvent control) kittens was that the toxicity was a result of oral ingestion of the solvent(s), but that a bad taste or some other unpleasant sensation associated with the active ingredients resulted in considerably less oral ingestion of the test material in the Group A kittens.

This study is classified as **Supplementary** as a companion animal safety study (OPPTS 870.7200), as it does not demonstrate a 5X margin of safety associated with exposure to the solvents/inerts and the proposed use of the formulation (with actives) in 8 week old kittens.

**ACUTE TOX ONE-LINERS**

1. **DP BARCODE:** D338710
2. **PC CODES:** 129099 (Imidacloprid: 9.1%); 129032 (Pyriproxyfen: 0.9%)
3. **CURRENT DATE:** 5 September 2007
4. **TEST MATERIALS:** 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-On Formulation, a liquid with a specific gravity of 1.097 g/mL, Lot No. 99-901-66; also tested was the test material without the actives, a liquid with a specific gravity of 1.0674 g/mL, Lot No. 99-901-68.

| Study/Species/Lab Study # /Date | MRID | Results | Tox. Cat. | Core Grade |
|---|---|---|---|---|
| Companion animal safety / 8-week old kitten/ Intervet Inc., DeSoto, KS /Project ID 75120 (150.851) / 8-JUN-2001 | 47089401 | 2 groups, each containing 7M & 7F 8-week old domestic short-hair cats were used. Kittens in Group A were treated with 5X application levels of the formulation containing the actives on Days 0, 7, 14, 21. Kittens in Group B were treated with ~5.6X application levels of the formulation without the actives. Two male kittens in Group B had adverse reactions (dilated pupils, generalized tremors, rapid breathing) and were euthanized on Day 1. At gross necropsy both had distended urinary bladders. On microscopic examination both showed necrosis of the external granular layer of the cerebellum. A number of Day 1 hematology & clinical chemistry changes were seen in the two dead kittens (increased neutrophil counts, decreased calcium, phosphorus, increased ALP, AST & ALT). Some other Group B kittens (but no group A kittens) had tremors following Day 7 and 21 treatment, with suggestive changes in clinical chemistry parameters. Study does not demonstrate 5X safety factor for exposure to solvents/inerts of this formulation. | N/A | S |

**Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived, I = Invalid**

*Inert ingredient information may be entitled to confidential treatment*

**EPA Primary Reviewer: Byron T. Backus, Ph.D.**
**Technical Review Branch, Registration Division (7505P)**
**EPA Secondary Reviewer: Masih Hashim, D.V.M., Ph.D.**
**Technical Review Branch, Registration Division (7505P)**

**Signature:** Byron T. Backus
**Date:** 9/06/2007
**Signature:** M. Hashim 9/6/07
**Date:**

**DATA EVALUATION RECORD**

**STUDY TYPE: Companion Animal Safety - Kittens (OPPTS 870.7200)**

**PC CODES: [129099 (Imidacloprid); 129032 (Pyriproxyfen)] – Not tested in this study**

**DP BARCODE: D338710**

**DECISION NO.: 215319**

**RISK MANAGER: (EPA): 01**

**TEST MATERIAL AND PRODUCT:** The proposed product contains Imidacloprid (9.1%) and Pyriproxyfen (0.46%), as well as one or more solvents. What was tested in this study was the formulation without active ingredients, [redacted]

**CITATION:** Abraham, A. S. (2001). Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-on with 5.0% Water Blank Formulation in the Target Species, 8-Week Old Kittens. Performing Laboratory: Intervet Inc. (formerly a facility owned and operated by Bayer Corporation Agriculture Division Animal Health), DeSoto Research Facility, DeSoto, Kansas 66018. Laboratory Project ID 75190 (150.828). Study Dated May 10, 2001. MRID 47089403. 165 p. + a 2 p. confidential appendix.

**SPONSOR:** Bayer Corporation Agriculture Division

**SUBMITTER:** Bayer HealthCare LLC, Animal Health Division, P.O. Box 390, Shawnee, KS 66201

**EXECUTIVE SUMMARY:** In a companion animal safety study (MRID 47089403), there were two groups, each containing 8 male and 8 female kittens (from 7 weeks 6 days to 8 weeks old at first dosing; day -1 bodyweights: males: 1.55-1.99 lbs; females: 1.47-1.96 lbs; source: Liberty Research Inc., Waverly, NY). Kittens in Group A were treated with the proposed formulation without the actives [redacted] at 5X the label indicated exposure rate for solvents (5 x [0.4 – 0.04] mL = 1.8 mL; this does not correct for [redacted] while kittens in Group B received no treatment and served as controls.

The dose was applied topically on the backside of the head and the neck of each kitten to avoid runoff. Kittens were treated on Days 0, 7, 14 and 21; the proposed label indicates once-a-month treatment, so that each of the kittens in Group A received a cumulative total of 20X of the proposed monthly dosage of the formulation solvents. Kittens in Group B received no exposure to any test material. On Day 13 the heaviest kitten in Group A weighed 2.51 lbs, so none had reached a weight >9 lbs (4.1 kg) which would have resulted in an increase in the 1X dose from 0.36 to 0.72 mL (Day 13 weights were used to set the dosages for Days 14 and 21).

On the days of dosing (Days 0, 7, 14 and 21) each kitten was observed five times, once prior to dosage and then at hourly intervals for four hours after application. Otherwise, clinical observations were made twice a day. Individual daily food consumption was determined visually, using a scoring system (≥75% consumption = 1, 25-75% consumption = 2, ≤25% consumption = 3). The kittens

were weighed six times before and during the study (Days -14, -7, -1, 13, 28 and 35). Blood samples were taken on Days -7, -1, 1, 22, and 35. Blood samples were also collected from one or more kittens on study days -5, 23 and 36, because either insufficient blood had been collected the previous day or there had been clotting in the previous day's sample. Prothrombin time and activated partial thromboplastic time measurements were not done because of the comparatively large amount of blood required for these tests and the age of the kittens; this protocol deviation had been previously discussed with and accepted by the Agency.

Two Group A kittens (male #811, female #816, from the same litter) had adverse reactions to the test material (formulation solvents) and were euthanized on Day 1. Signs observed following dosage in male #811 were salivation; no signs (other than rough coat, observed in all Group A kittens following treatment) were observed in the 4 hours following dosage for female #816. Signs of toxicity on Day 1 in male #811 were tremors, incoordination, unsteadiness, apprehensiveness, depression and dilated pupils. Signs of toxicity on Day 1 in female #816 were rapid respiration, apprehensiveness, incoordination, tremors, depression, seizure and dilated pupils. In the blood samples taken on day 1 both of these kittens showed a number of physiologically significant blood chemistry changes, including increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), and decreases in phosphorus (P) and calcium (Ca). Both also showed an increase (72-82%) in neutrophils from the Day -1 measurement. Kitten #811 showed an approximately 30% drop in potassium (K) from the Day -1 measurement. At gross necropsy both had distended urinary bladders, mottled (red and tan) livers, and pale kidneys. On microscopic examination, both showed necrosis in the external granular layer of the cerebellum.

There were no observed signs of treatment-related toxicity in other Group A kittens following the Day 0 treatment, including female #814, which was a littermate of #811 and #816. However, following the Day 7 treatment female #814 was unsteady and had tremors on Day 8, had tremors, circling and slowness on Day 9, and showed unsteadiness and sneezing on Day 10, but recovered on Day 11. None of the Group A kittens (including #814) showed signs of toxicity following treatment on Days 14 and 21. Kitten #814 had some clinical chemistry values (including elevated values for ALP, AST and ALT) on Day 1 similar – but not as pronounced – to those seen in #811 and #816.

Group A kittens all showed a rough hair coat (localized effect?) following applications on Days 0, 7, 14 and 21. Both Group A and Group B kittens showed sporadic episodes of loose (soft) stools, and Group A male #828 vomited prior to dosing on Day 14.

This study is classified as **Supplementary** as a companion animal safety study (OPPTS 870.7200), because it did not include testing of the proposed formulation with actives and because it does not indicate an adequate (5X) margin of exposure exists between the application rate exposure level to the solvent(s) of the proposed product and that which can result in the death of some kittens. The results of this study are consistent with the findings of the study in MRID 47089401, in which two kittens dosed at 5.6X with the solvent control formulation died following treatment on Day 0.

*Inert ingredient information may be entitled to confidential treatment*

**COMPLIANCE**: Signed and dated Quality Assurance (p. 4), [No] Data Confidentiality (p. 2) and Good Laboratory Practice Compliance (p. 3) statements are present.

## I. MATERIAL

MATERIALS

1. Test material: The test material without the 2 active ingredients (9.1% Imidacloprid and 0.46% Pyriproxyfen), [redacted]
   Description: A liquid, specific gravity not reported.
   Lot No.: 99-901-101.
   Storage: Stored in amber glass bottles at room temperature.
   Placebo: None (controls were not exposed to any test substance)
   Description: N/A
   Lot No.: N/A
   Storage: N/A

2. Administration: Topically applied to the backside of the head and the neck of each kitten to avoid run off.

3. Test animals
   Species: Cat
   Breed: Domestic Short hair
   Ages and weights at study initiation (Day 0 for ages, Day -1 for weights): 7 weeks 6 days to 8 weeks; males: 1.55 to 1.99 lbs; females: 1.47 to 1.96 lbs.
   Source: Liberty Research Inc., Waverly, NY
   Vaccinations and other medications: The kittens had been vaccinated with a four way feline vaccine, Fel-O-Vax IV (Feline Rhinotracheitis, Calici, Panleukopenia, Chlamydia Psittaci, Killed Virus and Chlamydia) on Study Days -14 and -7. All the kittens had been treated for coccidiosis once daily orally with Albon Suspension (Sulfadimethoxine) from study day -14 through study day -7. On Study Day -14, each kitten received approximately 25 mg of Sulfadimethoxine per pound of body weight. From Study Day -13 to -7 each kitten received approximately 12.5 mg of Sulfadimethoxine per pound of body weight/day.
   Housing: individual in cages with approximately 7.5 $ft^2$ of floor space per cage.
   Diet: Harlan Teklad® (commercial dry cat feed) and a canned kitten food (Feline Growth) from Hill's Pet Nutrition, Kansas City, MO. (fed once daily, however, no information is provided as to the amount that was offered). The kittens were fed with canned food until Day 22.
   Water: Tap water, *ad libitum*
   Environmental conditions:
   Temperature: (not stated)
   Humidity: (not stated)
   Air changes: (not stated)
   Photoperiod: 9-14 hours of lighting/day
   Acclimation period: 14 days

## II. STUDY DESIGN

### A. IN LIFE DATES

From the report (p. 12 of MRID 47089403) Day 0 was December 13, 1999. The experimental phase of the study was completed on February 28, 2000 (histopathology slides read).

*Inert ingredient information may be entitled to confidential treatment*

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

From p. 14 of MRID 47089403: "Thirty-two animals [out of a total of 44] were randomly allocated to two groups. Animals were blocked by sex and ranked by ascending order of study day -1 body weight and assigned a random number. From the first block (female), the animal with the larger of the first two random numbers was assigned to Group A (test substance), and the smaller to Group B (negative controls) and so forth until all the animals in the same sex were assigned. This procedure was repeated for the males..."

From p. 19 of MRID 47089403: "Eight males and eight females in group A were dosed with 5 times the monthly use rate volume (1.8 mL for kittens up to 9 lbs) of test substance. This resulted in a 20X (5X per week for four consecutive weeks) the monthly use volume of vehicle applied in a month's time... Eight males and eight females in Group B received no treatment and served as negative controls."

From p. 19 of MRID 47089403: "The dose was administered topically on the backside of the head and the neck of each kitten [in Group A] to avoid run off of test substance... The kittens [in Group A] were dosed four times, on study days 0, 7, 14, and 21."

**TABLE 1. Study design**

| Group & Weight Range (lb) | | Number of kittens | Mean Kitten Weight | | | |
|---|---|---|---|---|---|---|
| | | | Mean Kitten Wt ± S.D. (lb) on Day -1 (before 1st application) | Mean Kitten Wt ± S.D. (lb) on Day 13 (before 3rd application) | Mean Kitten Wt ± S.D. (lb) on Study Day 28 | Mean Kitten Wt ± S.D. (lb) on Study Day 37 |
| (A): 5X solvent | males ≤ 9 lb | 8* | 1.75 ± 0.13 | 2.32 ± 0.11 | 2.96 ± 0.14 | 3.28 ± 0.16 |
| | females ≤ 9 lb | 8* | 1.70 ± 0.17 | 2.22 ± 0.22 | 2.79 ± 0.20 | 3.05 ± 0.19 |
| | combined ≤ 9 lb | 16** | 1.72 ± 0.15 | 2.27 ± 0.18 | 2.88 ± 0.18 | 3.17 ± 0.21 |
| (B): no treatment | males ≤ 9 lb | 8 | 1.74 ± 0.13 | 2.33 ± 0.08 | 2.99 ± 0.08 | 3.34 ± 0.08 |
| | females ≤ 9 lb | 8 | 1.71 ± 0.17 | 2.21 ± 0.18 | 2.80 ± 0.21 | 3.11 ± 0.25 |
| | combined ≤ 9 lb | 16 | 1.72 ± 0.15 | 2.27 ± 0.15 | 2.90 ± 0.18 | 3.22 ± 0.21 |

Data calculated from information on p. 32 and 34 of MRID 47089403.
*7 kittens on Days 13, 28 and 38, as two kittens had been euthanized on Day 1.
**14 kittens on Days 13, 28 and 38, as two kittens had been euthanized on Day 1.

C. DOSE SELECTION RATIONALE

From p. 11 of MRID 47089403: "The study was conducted to evaluate the safety of 9.1% Imidacloprid with 0.46% Pyriproxyfen (w/w) spot-on [redacted] on kittens applied at 5 times the use volume at weekly intervals for a total of 4 weeks. This study was designed as a limit test and a full study with three dose levels at 1X, 3X and 5X was not conducted. Only blank formulation without active ingredient group was included in the study..."

*Inert ingredient information may be entitled to confidential treatment*

D. EXPERIMENTAL DESIGN

There were two groups, each initially containing 8 male and 8 female kittens (from 7 weeks 6 days to 8 weeks old; day -1 bodyweights: males: 1.55-1.99 lbs; females: 1.47-1.96 lbs). Kittens in Group A were treated with the proposed product without the actives [redacted] at 5X the label-specified use exposure rate for solvents (5 x [0.4-0.04 mL] = 1.8 mL) while kittens in Group B were not treated with anything. The dose was applied topically on the backside of the head and the neck of each kitten in Group A to avoid runoff. The dose was administered by parting the hair and using a syringe without a needle. Kittens were treated on Days 0, 7, 14 and 21; since the proposed label indicates once-a-month treatment, each of the kittens in Group A received a cumulative total of 20X of the proposed monthly dosage of the formulation solvents. Group B kittens served as negative controls.

At the last weighing (Day 35) the heaviest kitten weighed 3.54 lbs, so none had reached a weight >9 lbs (4.1 kg) which would have resulted in an increase in the 5X dose from 2.0 to 4.0 mL.

On the days of dosing (Days 0, 7, 14 and 21) each kitten was observed five times, once prior to dosage and then at hourly intervals for four hours after application. Otherwise, clinical observations were made twice (once in the a.m., once in the p.m.) a day. Individual daily food consumption was determined visually, using a scoring system ($\geq$75% consumption = 1, 25-75% consumption = 2, $\leq$25% consumption = 3). The kittens were weighed at six times before and during the study (Days -14, -7, -1, 13, 28 and 35). Blood samples were taken on Days -7, -1, 1, 22, and 35. It was necessary to obtain additional blood samples from individual kittens on study days -5, 23 and 36 due to insufficient quantities initially obtained or because of blood sample clotting. Prothrombin time and activated partial thromboplastic time measurements were not done because of the comparatively large amount of blood required for these tests and the age of the kittens; this protocol deviation had been previously discussed with and accepted by the Agency.

From p. 21 of MRID 47089403: "Physical examinations were performed on the study animals on study days -14, -1, and 35."

E. CLINICAL PATHOLOGY PARAMETERS

Blood samples were collected from each kitten on study Days -7, -1, 1, 22 and 35. There is no indication within the report that kittens were fasted prior to collection of blood. The CHECKED (X) parameters were examined:

a. Hematology

| X | | X | |
|---|---|---|---|
| X | Hematocrit (HCT)* | X | Leukocyte differential count* |
| X | Hemoglobin (HGB)* | X | Absolute and percent basophil count |
| | | X | Absolute and percent eosinophil count |
| X | Leukocyte count (WBC)* | X | Absolute and percent lymphocyte count |
| X | Erythrocyte count (RBC)* | X | Absolute and percent monocyte count |
| | | X | Absolute and percent neutrophil count |
| X | Platelet count (PLTS) | X | Mean corpuscular HGB (MCH)* |
| | Blood clotting measurements | X | Mean corpusc. HGB conc.(MCHC)* |
| | (Thromboplastin time) | X | Mean corpusc. volume (MCV)* |
| | (Clotting time) | | |
| | (Prothrombin time [PT])* | | |
| | (Activated partial thromboplastin time [APTT])* | | |

*Recommended in OPPTS 870.7200 Guidelines. The Prothrombin time and Activated partial thromoplastin time were not done because of the comparatively large volume of blood required for these tests and the age of the kittens. This deviation had been accepted by the Agency prior to initiation of this study.

b. Clinical chemistry

| X | ELECTROLYTES | X | OTHER |
|---|---|---|---|
| X | Calcium* | X | Albumin (Alb)* |
| X | Chloride* | X | Creatinine (Crea)* |
| | Magnesium | X | Blood urea nitrogen (BUN)* |
| X | Phosphorus* | | Total Cholesterol |
| X | Potassium* | X | Globulin (Glob)* |
| X | Sodium* | X | Glucose (Gluc)* |
| | | X | Total bilirubin (T Bil)* |
| | ENZYMES | X | Direct bilirubin (D Bil)* |
| | | | Total protein (TP)* |
| X | Alkaline phosphatase(ALP or ALK)* | | Triglycerides |
| | Cholinesterase(ChE) | | Serum protein electrophoresis |
| | Creatine phosphokinase | X | Albumin/Globulin (A/G) ratio |
| | Lactic acid dehydrogenase(LDH) | | Lipase |
| X | Serum alanine aminotransferase (ALT or SGPT)* | | |
| X | Serum aspartate aminotransferase(AST or SGOT)* | X | BUN/Creatinine ratio |
| | | X | Ca/Phos Ratio |
| | Gamma glutamyl transpeptidase(GGT) | X | Na/K Ratio |
| | Amylase | | |

*Recommended in OPPTS 870.7200 Guidelines.

*Inert ingredient information may be entitled to confidential treatment*

F. CONCOMITANT MEDICATIONS/THERAPIES

From p. 19 of MRID 47089403: "All the kittens were treated for coccidiosis once daily orally with Albon Suspension (Sulfadimethoxine) from study day -14 through study day -7. On study day -14, the animals received approximately 25 mg of Sulfadimethoxine per pound of body weight. Subsequent days (study day -13 to -7) the animals received approximately 12.5 mg of Sulfadimethoxine per pound of body weight."

G. STATISTICS

Although means and standard deviations were calculated for some parameters (such as body weight), statistical tests were primarily applied to chemistry and hematology pathology parameters. From p. 143 of MRID 47089403: "This study is intended to confirm the general safety of the vehicle and approximately the same number of adverse effects is expected between the two groups. Adverse effects will be summarized in tables. Certain types of adverse effects may be grouped together, depending on the clinical presentation, such as all effects, all transient effects or all blood chemistry effects. If the number or pattern of effects elicit clinical interest, incidence rates will also be compared between groups." For the clinical pathology parameters, it is stated (p. 21 of MRID 47089403): "For each animal, a baseline value was calculated for each clinical pathology test, by averaging the two pretreatment measurements (study days -7 and -1). Each clinical pathology test was then analyzed with a multivariate repeated measures ANOVA (baseline, study days 1, 22, and 35) including terms for Group, Sex, Animal (random), Day, and Group*Day as the predictors..."

H. DISPOSITION OF ANIMALS

From p. 14 of MRID 47089403: "Twelve animals not included in the experimental phase of the study were euthanized on December 13, 1999. Two [Group A] kittens were euthanized on December 14. [19]99 (Study Day 1). Twenty-nine animals in the experimental phase of the study were euthanized on January 21, 2000. One animal in the experimental phase of the study was given for adoption as pet." According to the OPPTS 870.7200 Guidelines: "Routine sacrifice or necropsy is not required for surviving animals."

I. COMPLIANCE

Signed and dated Quality Assurance [p. 4], [No] Data Confidentiality [p. 2], and Good Laboratory Practice (GLP) Compliance [p. 3] Statements were present.

## III. RESULTS

A. EXPOSURE LEVELS

Refer to Table 1 of this DER. Kittens in the control group (Group B), all weighing ≤ 9.0 lb, were not dosed, while kittens in the test group (Group A), also all weighing < 9.0 kg, were dosed with 1.8 mL of the formulation without actives [redacted] at each application. Applications were made on Days 0, 7, 14 and 21.

B. MORTALITY

Two Group A (male #811, female #816) kittens were euthanized during the afternoon of Day 1; all other kittens survived the 35-day observation period.

C. CLINICAL SIGNS

Group A: One male (#808) showed salivation at 3 hours post-dosing on Day 0. All kittens in Group A showed a rough hair coat at the 4 observations following dosage. One female (#823) and one male (#828) had loose stools on Day 1. Two kittens showed severe clinical signs on Day 1: male #811 had tremors, incoordination, unsteadiness, apprehension, depression and dilated pupils, while female #816 had rapid respiration, apprehension, incoordination, tremors, depression, seizures and dilated pupils. Both kittens showing severe clinical signs were euthanized during the afternoon of Day 1. Female #814 had loose stools on Day 4. Female #814 was unsteady and had tremors on Day 8, tremors, circling and slowness on Day 9, and unsteadiness and sneezing on Day 10. Group A kittens had rough hair coats following treatments on Days 7, 14 and 21.

Group B: Four kittens each had loose stools on three occasions during the period from study day 1 to 4. One kitten had loose stools on Day 14.

**TABLE 2a. Observed Signs of Toxicity After First Application (Day 0)**

| Group | Signs in the 4-hour observation period | Signs in the 1-3 days following treatment |
|---|---|---|
| **5X Vehicle (A)** | Diarrhea in one female (#814)<br>Sneezing in one male (#808)<br>Salivation in one male (#811)<br>Loose (soft) stool in one male (#828)<br>All treated kittens with rough hair coat following application. | Female #816 on study day 1: rapid respiration, apprehensiveness, incoordination, tremors, depression, seizure, dilated pupils – euthanized 3:20 PM.<br>Male #811 on study day 1: tremors, incoordination, unsteadiness, apprehensiveness, , depression, dilated pupils – euthanized 3:19 PM<br>Female #823 & Male #828: Loose stools |
| **No Treatment (B)** | Loose (soft) stools in females #815, #847.<br>Diarrhea in male #821. | Four kittens (females #813, #815, and #847; male # 821) with loose (soft) stools on days 1 and/or 2 and/or 3 and/or 4. |

Data from information on p. 37 of MRID 47089403.

| TABLE 2b. Observed Signs of Toxicity After Second Application (Day 7) | | |
|---|---|---|
| **Group** | **Signs in the 4-hour observation period** | **Signs in the 1-3 days following treatment** |
| **5X Vehicle (A)** | All treated kittens with rough hair coat following application. | Female #814: unsteadiness & tremors on day 8; tremors, circling, slowness on day 9; unsteadiness & sneezing on day 10 |
| **No Treatment (B)** | None | None. |

Data from information on p. 38 of MRID 47089403.

| TABLE 2c. Observed Signs of Toxicity After Third Application (Day 14) | | |
|---|---|---|
| **Group** | **Signs in the 4-hour observation period** | **Signs in the 1-3 days following treatment** |
| **5X Vehicle (A)** | All treated kittens with rough hair coat following application. | None. |
| **No Treatment (B)** | Male #821: loose (soft) stools on day 14. | None. |

Data from information on p. 38 of MRID 47089403.

| TABLE 2d. Observed Signs of Toxicity After Fourth Application (Day 21) | | |
|---|---|---|
| **Group** | **Signs in the 4-hour observation period** | **Signs in the 1-3 days following treatment** |
| **5X Vehicle (A)** | All treated kittens with rough hair coat following application. | None. |
| **No Treatment (B)** | None. | None. |

Data from information on p. 38 of MRID 47089403.

D. NEUROLOGICAL OBSERVATIONS

Some of the effects (tremors, disorientation, dilated pupils) observed in Group A kittens were consistent with neurotoxicity

E. BODY WEIGHT AND WEIGHT GAIN

All surviving kittens (in both groups) had good weight gains from day -1 to 13, from day 13 to 28, and again from day 28 to 35.

F. FOOD CONSUMPTION

No information is provided as to the exact (or even approximate) amount of food that was offered to kittens on a daily basis. As agreed with EPA, the amount of food consumed was determined visually, with 1 representing $\geq$ 75% offered food consumed, 2 being 25-75% consumption, and 3 representing <25% consumption. Most of the food consumption values were "1." The only value of "3" in Group A (vehicle treated kittens) after Day 0 was with female #816 on day 1 (the day this kitten was euthanized). A number of other Group A kittens (#814, #846 and #811) had values of "2" on day 1, but so did a number of group B kittens (#835, #818 and #821). Group A female #814 had a value of "2" on days 9 and 15, group A male #833 had a value of "2" on day 16, and group A female #846 had a value of "2" on day 23; otherwise, all group A kittens had values of "1" for food consumption in the period from day 2 to 35.

G. HEMATOLOGY

Day 1 neutrophil counts were noticeably elevated from their Day -1 values in the two euthanized kittens, #811 and #816 (kitten #811: 6.44 x $10^3$/µL on Day -1; 11.71 x $10^3$/µL on Day 1; kitten #816: 13.4 x $10^3$/µL on Day -1; 23.03 x $10^3$/µL on Day 1).

H. CLINICAL CHEMISTRY

In the two Group A kittens (#811 and #816) which were euthanized on Day 1, there were a number of physiologically significant blood chemistry changes, including increases in glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline

phosphatase (ALP), and decreases in potassium (K), phosphorus (P) and calcium (Ca).

**TABLE 3. Selected Hematology and Blood Chemistry Values for Kittens Euthanized on Day 1**

| Kitten + Parameter | Day -7 Value | Day -1 Value | Day 1 Value |
|---|---|---|---|
| **#811:** | | | |
| **Neutrophils** | 6.77 x $10^3$/µL | 6.44 x $10^3$/µL | **11.71 x $10^3$**/µL |
| **Glucose** | 110 mg/dL | 125 mg/dL | **134** mg/dL |
| **Potassium (K)** | 5.7 mmol/L | 4.8 mmol/L | **4.5** mmol/L |
| **Phosphorus (P)** | 9.8 mg/dL | 9.3 mg/dL | **6.2** mg/dL |
| **Calcium (Ca)** | 11.2 mg/dL | 11.9 mg/dL | **5.1** mg/dL |
| **ALP** | 94 u/L | 100 u/L | **156** u/L |
| **AST** | 19 u/L | 22 u/L | **243** u/L |
| **ALT** | 35 u/L | 39 u/L | **360** u/L |
| **#816:** | | | |
| **Neutrophils** | 9.81 x $10^3$/µL | 13.4 x $10^3$/µL | **23.03 x $10^3$**/µL |
| **Glucose** | 91 mg/dL | 111 mg/dL | **188** mg/dL |
| **Potassium (K)** | 7.2 mmol/L | 6.9 mmol/L | **4.8** mmol/L |
| **Phosphorus (P)** | 10.9 mg/dL | 10.8 mg/dL | **4.9** mg/dL |
| **Calcium (Ca)** | 11.7 mg/dL | 12.5 mg/dL | **5.3** mg/dL |
| **ALP** | 125 u/L | 105 u/L | **197** u/L |
| **AST** | 24 u/L | 26 u/L | **633** u/L |
| **ALT** | 33 u/L | 35 u/L | **1333** u/L |

Data from information on p. 71 & 75 of MRID 47089403.

Group A female #814, which had symptoms (including tremors) on days 8-10, had slight decreases in blood phosphorus and calcium, and noticeable increases in ALP, AST and ALT on Day 1, but these values were normal for this kitten on Day 22. Kitten #814 is identified (p. 31 of MRID 47089403) as being a littermate of #811 and #816. None of the remaining kittens from this litter was in Group A (#813 and #815 were in Group B; #812 was received but not included in this study).

**TABLE 4. Selected Hematology and Blood Chemistry Values for #814**

| Kitten + Parameter | Day -7 | Day -1 | Day 1 | Day 22 | Day 35 |
|---|---|---|---|---|---|
| **#814:** | | | | | |
| **Neutrophils** | 7.09 x$10^3$/µL | 11.93x$10^3$/µL | **13.37x$10^3$**/µL | 9.41 x $10^3$/µL | 8.88 x $10^3$/µL |
| **Glucose** | 80 mg/dL | 91 mg/dL | 89 mg/dL | 96 mg/dL | 87 mg/dL |
| **Potassium (K)** | 6.3 mmol/L | 6.6 mmol/L | **5.8** mmol/L | 6.7 mmol/L | 7.6 mmol/L |
| **Phosphorus (P)** | 9.4 mg/dL | 11 mg/dL | **8** mg/dL | 10 mg/dL | 9.9 mg/dL |
| **Calcium (Ca)** | 12.2 mg/dL | 12.9 mg/dL | **10.4** mg/dL | 11.8 mg/dL | 11.6 mg/dL |
| **ALP** | 41 u/L | 27 u/L | **95** u/L | 25 u/L | 22 u/L |
| **AST** | 41 u/L | 27 u/L | **95** u/L | 25 u/L | 22 u/L |
| **ALT** | 50 u/L | 57 u/L | **157** u/L | 60 u/L | 55 u/L |

Data from information on p. 73 of MRID 47089403.

*Inert ingredient information may be entitled to confidential treatment*

I. NECROPSY FINDINGS

At gross necropsy both of the kittens which were euthanized on Day 1 had distended urinary bladders. On microscopic examination, both showed necrosis in the external granular layer of the cerebellum. Other findings were incidental and/or considered to be secondary to the moribund condition of the kittens.

## IV. DISCUSSION

In a companion animal safety study (MRID 47089403), there were two groups, each containing 8 male and 8 female kittens (from 7 weeks 6 days to 8 weeks old at first dosing; day -1 bodyweights: males: 1.55-1.99 lbs; females: 1.47-1.96 lbs; source: Liberty Research Inc., Waverly, NY). Kittens in Group A were treated with the proposed formulation without the actives [redacted] at 5X the label indicated exposure rate for solvents (5 x [0.4 – 0.04] mL = 1.8 mL; this does not correct for [redacted] while kittens in Group B received no treatment and served as controls.

The dose was applied topically on the backside of the head and the neck of each kitten to avoid runoff. Kittens were treated on Days 0, 7, 14 and 21; the proposed label indicates once-a-month treatment, so that each of the kittens in Group A received a cumulative total of 20X of the proposed monthly dosage of the formulation solvents. Kittens in Group B received no exposure to any test material. On Day 13 the heaviest kitten in Group A weighed 2.51 lbs, so none had reached a weight >9 lbs (4.1 kg) which would have resulted in an increase in the 1X dose from 0.36 to 0.72 mL (Day 13 weights were used to set the dosages for Days 14 and 21).

On the days of dosing (Days 0, 7, 14 and 21) each kitten was observed five times, once prior to dosage and then at hourly intervals for four hours after application. Otherwise, clinical observations were made twice a day. Individual daily food consumption was determined visually, using a scoring system (≥75% consumption = 1, 25-75% consumption = 2, ≤25% consumption = 3). The kittens were weighed six times before and during the study (Days -14, -7, -1, 13, 28 and 35). Blood samples were taken on Days -7, -1, 1, 22, and 35. Blood samples were also collected from one or more kittens on study days -5, 23 and 36, because either insufficient blood had been collected the previous day or there had been clotting in the previous day's sample. Prothrombin time and activated partial thromboplastic time measurements were not done because of the comparatively large amount of blood required for these tests and the age of the kittens; this protocol deviation had been previously discussed with and accepted by the Agency.

Two Group A kittens (male #811, female #816, from the same litter) had adverse reactions to the test material (formulation solvents) and were euthanized on Day 1. Signs observed following dosage in male #811 were salivation; no signs (other than rough coat, observed in all Group A kittens following treatment) were observed in the 4 hours following dosage for female #816. Signs of toxicity on Day 1 in male #811 were tremors, incoordination, unsteadiness, apprehensiveness, depression and dilated pupils. Signs of toxicity on Day 1 in female #816 were rapid respiration, apprehensiveness, incoordination, tremors, depression, seizure and dilated pupils. In the blood samples taken on day 1 both of these kittens showed a number of physiologically significant blood chemistry changes, including increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), and decreases in phosphorus (P) and calcium (Ca). Both also showed an increase (72-82%) in neutrophils from the Day -1 measurement. Kitten #811 showed an approximately 30% drop in potassium (K) from the Day -1 measurement. At gross necropsy both had distended urinary bladders, mottled (red and tan) livers, and pale

kidneys. On microscopic examination, both showed necrosis in the external granular layer of the cerebellum.

There were no observed signs of treatment-related toxicity in other Group A kittens following the Day 0 treatment, including female #814, which was a littermate of #811 and #816. However, following the Day 7 treatment female #814 was unsteady and had tremors on Day 8, had tremors, circling and slowness on Day 9, and showed unsteadiness and sneezing on Day 10, but recovered on Day 11. None of the Group A kittens (including #814) showed signs of toxicity following treatment on Days 14 and 21. Kitten #814 had some clinical chemistry values (including elevated values for ALP, AST and ALT) on Day 1 similar – but not as pronounced – to those seen in #811 and #816.

Group A kittens all showed a rough hair coat (localized effect?) following applications on Days 0, 7, 14 and 21. Both Group A and Group B kittens showed sporadic episodes of loose (soft) stools, and Group A male #828 vomited prior to dosing on Day 14.

This study is classified as **Supplementary** as a companion animal safety study (OPPTS 870.7200), because it did not include testing of the proposed formulation with actives and because it does not indicate an adequate (5X) margin of exposure exists between the application exposure level to the solvent(s) of the proposed product and that which can result in the death of some kittens. The results of this study are consistent with the findings of the study in MRID 47089401, in which two kittens dosed at 5.6X with the solvent control formulation died following treatment on Day 0.

**ACUTE TOX ONE-LINERS**

1. **DP BARCODE:** D338710
2. **PC CODES:** N/A (solvents only tested)
3. **CURRENT DATE:** 6 September 2007
4. **TEST MATERIAL:** The proposed product contains Imidacloprid (9.1%) and Pyriproxyfen (0.46%), as well as one or more solvents. What was tested in this study was the formulation without active ingredients, [redacted] [redacted]

| Study/Species/Lab Study # /Date | MRID | Results | Tox. Cat. | Core Grade |
|---|---|---|---|---|
| Companion animal safety / 8-week old kitten / Intervet Inc., DeSoto, KS / Project ID 75190 (150.828) / 10-MAY-2001 | 47089403 | 2 groups, each containing 8M & 8F 8-week old domestic short-hair kittens were used. Kittens in Group A were treated with 5X application levels (=1.8mL) of the formulation without actives on days 0, 7, 14 & 21; kittens in Group B were not treated. Two Group A kittens (1M & 1F) had adverse reactions (tremors, incoordination, dilated pupils) and were euthanized on Day 1. Both kittens showed a number of significant Day 1 blood chemistry changes including increases in ALP, AST, ALT and decreases in serum phosphorus and calcium. On microscopic examination, both showed necrosis in the external granular layer of the cerebellum. Group A kitten #814 had similar – but not as pronounced symptoms – following the Day 7 treatment but recovered by Day 11. Results of study show a less than 5X margin of safety between the application rate exposure level to the solvents and that which can result in death. | N/A | S |

**Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived, I = Invalid**

**EPA Primary Reviewer: Byron T. Backus, Ph.D.**
**Technical Review Branch, Registration Division (7505P)**
**EPA Secondary Reviewer: Masih Hashim, D.V.M., Ph.D.**
**Technical Review Branch, Registration Division (7505P)**

**Signature:** Byron T. Backus
**Date:** 9/6/2007
**Signature:** Masih Hashim
**Date:** 9/6/07

**DATA EVALUATION RECORD**

**STUDY TYPE: Companion Animal Safety - Kittens (OPPTS 870.7200)**

**PC CODES: [129099 (Imidacloprid); 129032 (Pyriproxyfen)] – Not tested in this study**

**DP BARCODE: D338710**

**DECISION NO.: 215319**

**RISK MANAGER: (EPA): 01**

**TEST MATERIAL AND PRODUCT:** The proposed product contains Imidacloprid (9.1%) and Pyriproxyfen (0.46%), as well as one or more solvents. What was tested in this study was the formulation without active ingredients, [redacted]

**CITATION:** Abraham, A. S. (2000). Evaluation of the General Safety of 9.1% Imidacloprid with 0.46% (W/W)% Pyriproxyfen Spot-on with 4.6% (W/W) Water Blank Formulation at Three Times the Use Rate Volume in the Target Species, 8-Week Old Kittens. Performing Laboratory: Bayer Corporation Agricultural Division Animal Health DeSoto Research Facility, DeSoto, Kansas 66018. Laboratory Project ID 75191 (150.937). Study Completion Date: October 19, 2000. MRID 47089405. 133 p. + a 2 p. confidential appendix.

**SPONSOR:** Bayer Corporation Agriculture Division

**SUBMITTER:** Bayer HealthCare LLC, Animal Health Division, P.O. Box 390, Shawnee, KS 66201

**EXECUTIVE SUMMARY:** In a companion animal safety study (MRID 47089405), there were two groups, each containing 7 male and 7 female kittens (from 7 weeks 5 days to 8 weeks old at first dosing; day -1 bodyweights: males: 1.48-2.14 lbs; females: 1.36-1.92 lbs; source: Liberty Research Inc., Waverly, NY). Kittens in Group A were treated with the proposed formulation without the actives [redacted] at 3X the label exposure rate for solvents (3 x [0.4 – 0.04] mL = ~1.1 mL; this does not correct for [redacted] while kittens in Group B received no treatment and served as controls.

The dose was applied topically on the backside of the head and the neck of each kitten to avoid runoff. Kittens were treated on Days 0, 7, 14 and 21; the proposed label indicates once-a-month treatment, so that each of the kittens in Group A received a cumulative total of 12X of the proposed monthly dosage of the formulation solvents. Kittens in Group B received no exposure to any test material. On Day 13 the heaviest kitten in Group A weighed 2.46 lbs, so none had reached a weight >9 lbs (4.1 kg) which would have resulted in an increase in the 1X dose from 0.36 to 0.72 mL (Day 13 weights were used to set the dosages for Days 14 and 21).

On the days of dosing (Days 0, 7, 14 and 21) each kitten was observed five times, once prior to dosage and then at hourly intervals for four hours after application. Otherwise, clinical observations were made twice a day. Individual daily food consumption was determined visually, using a scoring system (≥75% consumption = 1, 25-75% consumption = 2, ≤25% consumption = 3). The kittens

were weighed six times before and during the study (Days -14, -7, -1, 13, 28 and 35). Blood samples were taken on Days -7, -1, 1, 22, and 35. On all collection days, some kittens were rebled due to clotting of the initial sample. Prothrombin time and activated partial thromboplastic time measurements were not done because of the comparatively large amount of blood required for these tests and the age of the kittens; this protocol deviation had been previously discussed with and accepted by the Agency.

There were no mortalities, as all kittens survived to the termination of the study on Day 35. One Group A male (#893) showed signs (unsteadiness, tremors) of toxicity on Days 1-3; this kitten also showed significant decreases in phosphorus and calcium (41.9% and 40% respectively) on Day 1 from Day -1 levels. Kitten #893 also showed an increase in neutrophil count on Day 1 (Day -1: 11.09 x $10^3$/µL; Day 1: 18.94 x $10^3$/µL). Kitten #893 had no littermates in either Group A or B.

Two additional Group A kittens (#871 & #882) showed slight – but noticeable – decreases in phosphorus and calcium on Day 1 (#871: 27.8% and 8.5% respectively from Day -1 values; #882: 25.8% and 11.7% respectively from Day -1 values), and kitten #871 (but not #882) also showed an increase in neutrophil count on Day 1 (Day -1: 3.43 x $10^3$/µL; Day 1: 12.68 x $10^3$/µL).

A number of kittens (6 in Group A and 4 in Group B) had soft (loose) stools and/or diarrhea in the period from 1 to 6 days after the first dosage.

Following treatment on Day 7 Group A kitten #882 showed depression, slowness and dehydration. However, this kitten had diarrhea on Days 5 through 7; following the day 7 treatment #882 continued to show soft stools/diarrhea through Day 20. This kitten was treated for diarrhea and dehydration on days 7 through 9. These effects were not considered to be related to exposure to the test material.

Group A kittens all showed a rough hair coat (localized effect?) following applications on Days 0, 7, 14 and 21. This is not considered a toxic effect.

This study is classified as **Supplementary** as a companion animal safety study (OPPTS 870.7200) in 8 week-old kittens, in part because it did not involve actual testing of the proposed formulation with actives. This study was apparently conducted (at least in part) to establish the existence of a 3X safety factor with respect to the normal use application exposure levels of the solvent(s) of the proposed Imidacloprid-Pyriproxyfen formulation and the level at which toxicity occurs. As one of the 14 Group A kittens showed signs of toxicity (including unsteadiness and tremors) on Days 1-3 similar to those observed in kittens exposed to 5.6X or 5X levels of the solvent(s) in other studies (MRIDs 47089401 and 47089403) a 3X margin of safety was not established.

**COMPLIANCE:** Signed and dated Quality Assurance (p. 4), [No] Data Confidentiality (p. 2) and Good Laboratory Practice Compliance (p. 3) statements are present.

## I. MATERIAL

MATERIALS

1. Test material: The test material without the 2 active ingredients (9.1% Imidacloprid and 0.46% Pyriproxyfen), [redacted]

| | |
|---|---|
| Description: | A liquid, specific gravity not reported. |
| Lot No.: | 99-901-101. |
| Storage: | Stored in amber glass bottles at room temperature. |
| Placebo: | None (controls were not exposed to any test substance) |
| Description: | N/A |
| Lot No.: | N/A |
| Storage: | N/A |

2. Administration: Topically applied to the backside of the head and the neck of each kitten to avoid run off.
3. Test animals
Species: Cat
Breed: Domestic Short hair
Ages and weights at study initiation (Day 0 for ages, Day -1 for weights): 7 weeks 5 days to 8 weeks; males: 1.48 to 2.14 lbs; females: 1.36 to 1.92 lbs.
Source: Liberty Research Inc., Waverly, NY
Vaccinations and other medications: The kittens had been vaccinated with a four way feline vaccine, Fel-O-Vax® IV (Feline Rhinotracheitis, Calici-Panleukopenia-Chlamydia Psittaci Vaccine Killed Virus and Chlamydia) on Study Days -14 and --1. During the course of the study one kitten (#882) in Group A was treated for diarrhea and dehydration, as were two kittens (#883, #884) in Group B.
Housing: individual in cages with approximately 3.3 $ft^2$ of floor space per cage.
Diet: Harlan Teklad® (commercial dry cat feed) and a canned kitten food (Feline Growth) from Hill's Pet Nutrition, Kansas City, MO. (fed once daily, however, no information is provided as to the amount that was offered).
Water: Tap water, *ad libitum*
Environmental conditions:
Temperature: (not stated)
Humidity: (not stated)
Air changes: (not stated)
Photoperiod: 9-14 hours of lighting/day
Acclimation period: 14 days

## II. STUDY DESIGN

### A. IN LIFE DATES

From the report (p. 12 of MRID 47089403) Day 0 was January 13, 2000. The experimental phase of the study was completed on February 17, 2000.

### B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

From p. 12 of MRID 47089405: "Twenty-eight kittens were randomly allocated to two groups. Animals were blocked by sex and ranked by ascending order of study day -1 body weight, and assigned a random number. From the first block (female), the animal with the larger of the first two random numbers was assigned to Group A (vehicle), and the smaller to Group B (no treatment) and so forth until all the animals in the same sex were assigned. This procedure was repeated for the males..."

From p. 16 of MRID 47089405: "The volume of product that is active ingredients is approximately 10%. Therefore, for this study, the normal dose for a kitten less than 9 lbs would be 0.36 mL (90% of 0.4). Based on this product design, the exaggerated doses were based on dose volumes and a kitten weighing less than 9 lbs would receive (3 times 0.36 mL) 1.1 mL volume for each treatment."

From p. 17 of MRID 47089405: "Seven male and seven female kittens in Group A were dosed with an equivalent volume of vehicle at 3X the monthly use rate volume of a 9.1% imidacloprid with 0.46% pyriproxyfen formulation minus the active ingredients (1.1 mL / kitten weighing between 0 and 9 lbs)... Seven male and seven female kittens in Group B served as negative controls and were not treated."

*Inert ingredient information may be entitled to confidential treatment*

From p. 17 of MRID 47089405: "The dose was administered topically on the back of the head and neck to avoid dose run off of the vehicle. of each kitten [in Group A] to avoid run off. The kittens [in Group A] were dosed four times, on study days 0, 7, 14, and 21."

**TABLE 1. Study design**

| Group & Weight Range (lb) | | Number of kittens | Mean Kitten Weight: Mean Kitten Wt ± S.D. (lb) on Day -1 (before 1st application) | Mean Kitten Wt ± S.D. (lb) on Day 13 (before 3rd application) | Mean Kitten Wt ± S.D. (lb) on Study Day 28 | Mean Kitten Wt ± S.D. (lb) on Study Day 35 |
|---|---|---|---|---|---|---|
| (A): 5X solvent | males ≤ 9 lb | 7 | 1.77 ± 0.17 | 2.19 ± 0.23 | 2.81 ± 0.20 | 3.25 ± 0.24 |
| | females ≤ 9 lb | 7 | 1.60 ± 0.14 | 1.91 ± 0.21 | 2.51 ± 0.21 | 2.90 ± 0.21 |
| | combined ≤ 9 lb | 14 | 1.69 ± 0.17 | 2.05 ± 0.26 | 2.66 ± 0.25 | 3.08 ± 0.28 |
| (B): no treat-ment | males ≤ 9 lb | 7 | 1.75 ± 0.22 | 2.19 ± 0.18 | 2.81 ± 0.19 | 3.26 ± 0.17 |
| | females ≤ 9 lb | 7 | 1.66 ± 0.16 | 2.01 ± 0.30 | 2.58 ± 0.28 | 2.99 ± 0.28 |
| | combined ≤ 9 lb | 14 | 1.71 ± 0.19 | 2.10 ± 0.26 | 2.70 ± 0.26 | 3.13 ± 0.27 |

Data calculated from information on p. 28 and 29 of MRID 47089405.

C. DOSE SELECTION RATIONALE

From p. 9 of MRID 47089405: "This companion animal safety study was conducted to evaluate the general safety of 9.1% Imidacloprid with 0.46% Pyriproxyfen (W/W) with [redacted] on kittens applied at 3X use volume of the inert ingredients at weekly intervals for a total of 4 treatments in 8-week old kittens..."

D. EXPERIMENTAL DESIGN

There were two groups, each containing 7 male and 7 female kittens (from 7 weeks 5 days to 8 weeks old; day -1 bodyweights: males: 1.48-2.14 lbs; females: 1.36-1.92 lbs). Kittens in Group A were treated with the proposed product without the actives [redacted] at 3X the label-specified use exposure rate for solvents (3 x [0.4-0.04 mL] ~ 1.1 mL) while kittens in Group B were not treated with anything. The dose was applied topically on the backside of the head and the neck of each kitten in Group A to avoid runoff. The dose was administered by parting the hair and using a syringe without a needle. Kittens were treated on Days 0, 7, 14 and 21; since the proposed label indicates once-a-month treatment, each of the kittens in Group A received a cumulative total of 12X of the proposed monthly dosage of the formulation solvents. Group B kittens served as negative controls.

At the last weighing (Day 35) the heaviest kitten weighed 3.46 lbs, so none had reached a weight >9 lbs (4.1 kg) which would have resulted in an increase in the 3X dose from 1.2 to 2.4 mL.

On the days of dosing (Days 0, 7, 14 and 21) each kitten was observed five times, once prior to dosage and then at hourly intervals for four hours after application. Otherwise, clinical observations were made twice (once in the a.m., once in the p.m.) a day. Individual daily food consumption was determined visually, using a scoring system (≥75% consumption = 1, 25-75% consumption = 2, ≤25% consumption = 3). The kittens were weighed at six times before and during the study (Days -14, -7, -1, 13, 28 and 35).

Blood samples were taken on Days -7, -1, 1, 22, and 35. It was necessary to obtain additional blood samples from individual kittens on several days due to insufficient quantities initially obtained or because of blood sample clotting. Prothrombin time and activated partial thromboplastic time measurements were not done because of the comparatively large amount of blood required for these tests and the age of the kittens; this protocol deviation had been previously discussed with and accepted by the Agency.

From p. 18 of MRID 47089405: "Physical examinations were performed on the study animals on study days -10, -1, and 35."

E. CLINICAL PATHOLOGY PARAMETERS

Blood samples were collected from each kitten on study Days -7, -1, 1, 22 and 35. There is no indication within the report that kittens were fasted prior to collection of blood. The CHECKED (X) parameters were examined:

a. Hematology

| | | | |
|---|---|---|---|
| X | | X | |
| X | Hematocrit (HCT)* | X | Leukocyte differential count* |
| X | Hemoglobin (HGB)* | X | Absolute and percent basophil count |
| | | X | Absolute and percent eosinophil count |
| X | Leukocyte count (WBC)* | X | Absolute and percent lymphocyte count |
| X | Erythrocyte count (RBC)* | X | Absolute and percent monocyte count |
| | | X | Absolute and percent neutrophil count |
| X | Platelet count (PLTS) | X | Mean corpuscular HGB (MCH)* |
| | Blood clotting measurements | X | Mean corpusc. HGB conc.(MCHC)* |
| | (Thromboplastin time) | X | Mean corpusc. volume (MCV)* |
| | (Clotting time) | | |
| | (Prothrombin time [PT])* | | |
| | (Activated partial thromboplastin time [APTT])* | | |

*Recommended in OPPTS 870.7200 Guidelines. The Prothrombin time and Activated partial thromoplastin time were not done because of the comparatively large volume of blood required for these tests and the age of the kittens. This deviation had been accepted by the Agency prior to initiation of this study.

b. Clinical chemistry

| X | ELECTROLYTES | X | OTHER |
|---|---|---|---|
| X | Calcium* | X | Albumin (Alb)* |
| X | Chloride* | X | Creatinine (Crea)* |
| | Magnesium | X | Blood urea nitrogen (BUN)* |
| X | Phosphorus* | | Total Cholesterol |
| X | Potassium* | X | Globulin (Glob)* |
| X | Sodium* | X | Glucose (Gluc)* |
| | | X | Total bilirubin (T Bil)* |
| | ENZYMES | X | Direct bilirubin (D Bil)* |
| | | | Total protein (TP)* |
| X | Alkaline phosphatase(ALP or ALK)* | | Triglycerides |
| | Cholinesterase(ChE) | | Serum protein electrophoresis |
| | Creatine phosphokinase | X | Albumin/Globulin (A/G) ratio |
| | Lactic acid dehydrogenase(LDH) | | Lipase |
| X | Serum alanine aminotransferase (ALT or SGPT)* | | |
| X | Serum aspartate aminotransferase(AST or SGOT)* | X | BUN/Creatinine ratio |
| | | X | Ca/Phos Ratio |
| | Gamma glutamyl transpeptidase(GGT) | X | Na/K Ratio |
| | Amylase | | |

*Recommended in OPPTS 870.7200 Guidelines.

F. CONCOMITANT MEDICATIONS/THERAPIES

From p. 17 of MRID 47089405: "One kitten with diarrhea and suspected to have bacterial (negative for coccidian) enteritis was treated subcutaneously with Excenel at 1 mg per day for two days (study day -9 and -8). On study day 7 to 9, one kitten (#882 – group A) was treated for diarrhea and dehydration. Kitten #882 was treated subcutaneously with Excenel at 2 mg per day and 12 mL of Lactated Ringers Solution (Sodium Chloride 600 mg, Sodium Lactate 310 mg, Potassium Chloride 30 mg, Calcium Chloride Dihydrate 20 mg and Water for Injection q.s. per 100 mL) twice a day except one treatment on study day 9. On study day 7 and 8 one kitten (#883 – group B) was treated for diarrhea (negative for coccidian). Kitten #883 was treated subcutaneously with Excenel at 2 mg per day. On study day 13 and 14 one kitten (#884 – group B) was treated for diarrhea and dehydration. Kitten #884 was treated once a day subcutaneously with Excenel at 2 mg and 12 mL of Lactated Ringers Solution."

G. STATISTICS

Although means and standard deviations were calculated for some parameters (such as body weight), statistical tests were primarily applied to chemistry and hematology pathology parameters. From p. 113 of MRID 47089405: "This study is intended to confirm the general safety of the vehicle and approximately the same number of adverse effects is expected between the two groups. Adverse effects will be summarized in tables. Certain types of adverse effects may be grouped together, depending on the clinical presentation, such as all effects, all transient effects or all blood chemistry

effects. If the number or pattern of effects elicit clinical interest, incidence rates will also be compared between groups." For the clinical pathology parameters, it is stated (p. 19 of MRID 47089405): "For each animal, a baseline value was calculated for each clinical pathology test, by averaging the two pretreatment measurements (study days -7 and -1). Each clinical pathology test was then analyzed with a multivariate repeated measures ANOVA (baseline, study days 1, 22, and 35) including terms for Group, Sex, Animal (random), Day, and Group*Day as the predictors..."

H. DISPOSITION OF ANIMALS

From p. 12 of MRID 47089405: "One animal not included in the experimental phase of the study was euthanized due to poor health on December 30, 1999 (study day -14). One animal not included in the experimental phase of the study was euthanized due to poor health on January 03, 2000 (study day -10). One kitten was found dead on study day -10. The cause of death was due to dehydration and lack of nutrients due to enteritis of undetermined origin. Thirteen animals not included in the experimental phase of the study were euthanized on January 13, 2000 (study day 0). The remaining 28 animals included in the experimental phase of the study were not euthanized at the end of the study (February 17, 2000)." According to the OPPTS 870.7200 Guidelines: "Routine sacrifice or necropsy is not required for surviving animals."

I. COMPLIANCE

Signed and dated Quality Assurance [p. 4], [No] Data Confidentiality [p. 2], and Good Laboratory Practice (GLP) Compliance [p. 3] Statements were present.

## III. RESULTS

A. EXPOSURE LEVELS

Refer to Table 1 of this DER. Kittens in the control group (Group B), all weighing ≤ 9.0 lb, were not dosed, while kittens in the test group (Group A), also all weighing ≤ 9.0 kg, were dosed with 1.1 mL of the formulation without actives [redacted] at each application. Applications were made on Days 0, 7, 14 and 21.

B. MORTALITY

There was no mortality. All kittens survived the 35-day observation period.

C. CLINICAL SIGNS

Group A: One male (#893) showed signs (unsteadiness, tremors, "proprioception deficit") of toxicity on Days 1-3, consistent with the signs observed in some kittens exposed to 5.6X and 5X in other studies (MRIDs 47089401 & 47089403). However, male #893 showed no signs of toxicity on Day 4 or subsequently (including after applications on Days 7, 14 and 21). Male #893 consumed <25% of the food that was offered on Day 2.

**TABLE 2a. Observed Signs of Toxicity After First Application (Day 0)**

| Group | Signs in the 4-hour observation period | Signs in the 1-3 days following treatment |
|---|---|---|
| **5X Vehicle (A)** | All treated kittens with rough hair coat following application except for males #886 and #893. One male (#886) and one female (#882) had soft (loose) stools before application. | Male #893 showed unsteadiness, tremors, "proprioception deficit." Five kittens (females #863, 882; males #864, #886, #888) showed soft (loose) stools or diarrhea. |
| **No Treatment (B)** | Diarrhea or soft stools in females #866 and #883. | Three kittens (females #866, #883, and #884) with loose (soft) stools and/or diarrhea on days 1 and/or 2 and/or 3. |

Data from information on p. 32 of MRID 47089405.

**TABLE 2b. Observed Signs of Toxicity After Second Application (Day 7)**

| Group | Signs in the 4-hour observation period | Signs in the 1-3 days following treatment |
|---|---|---|
| **5X Vehicle (A)** | All treated kittens with rough hair coat following application. One female (#882) with diarrhea, depression, slowness & dehydration prior to and after application. One male (#864) with soft stools prior to application. | Female #882: depression, dehydration and slowness on day 8; soft stools on day 9. One female (#860) with soft stools on day 9. |
| **No Treatment (B)** | Two females (#866, #883) with diarrhea and/or soft stools. | One female (#883) with soft stools on day 8. |

Data from information on p. 33 of MRID 47089405.

| TABLE 2c. Observed Signs of Toxicity After Third Application (Day 14) | | |
|---|---|---|
| **Group** | **Signs in the 4-hour observation period** | **Signs in the 1-3 days following treatment** |
| **5X Vehicle (A)** | All treated kittens with rough hair coat following application. One female (#882) with diarrhea prior to application; one male (#886) with soft stools prior to application. | Female #882 with diarrhea or soft stools; male #886 with soft stools. |
| **No Treatment (B)** | Female #884 with slowness (this female had diarrhea, depression & slowness on day 13). | Female #884 & male #867 with soft stools. |

Data from information on p. 33-34 of MRID 47089405.

| TABLE 2d. Observed Signs of Toxicity After Fourth Application (Day 21) | | |
|---|---|---|
| **Group** | **Signs in the 4-hour observation period** | **Signs in the 1-3 days following treatment** |
| **5X Vehicle (A)** | All treated kittens with rough hair coat following application. | Female #861 vomited on day 22. |
| **No Treatment (B)** | None. | Male #869 vomited on day 22. |

Data from information on p. 34-35 of MRID 47089405.

D. NEUROLOGICAL OBSERVATIONS

The effects (unsteadiness, tremors) observed in Group A male #893 were consistent with neurotoxicity, and with the signs seen in some kittens exposed to 5.6X and 5X the same formulation solvents/inerts in other studies (MRIDs 47089401 & 47089403).

E. BODY WEIGHT AND WEIGHT GAIN

Most kittens (in both groups) had good weight gains from day -1 to 13, from day 13 to 28, and again from day 28 to 35. One Group B kitten (female #884) had a slight weight loss in the period from Day -1 to 13 (from 1.44 lbs on Day -1 to 1.41 lbs on Day 13). This kitten had a number of occurrences of diarrhea or soft stools, and was dehydrated on Day 13. This kitten also consumed <25% of the offered food on Days 0 and 13 (these represented 2/3 of the occurrences of this among the 28 kittens in the study in the period from Day -12 to 35, the other being in Group A male #893 on Day 2).

F. FOOD CONSUMPTION

No information is provided as to the exact (or even approximate) amount of food that was offered to kittens on a daily basis. As agreed with EPA, the amount of food consumed was determined visually, with 1 representing ≥ 75% offered food consumed, 2 being 25-75% consumption, and 3 representing <25% consumption. Most of the food consumption values were "1," particularly after Day 14. The only value of "3" in Group A (vehicle treated kittens) after Day 0 was with male #893 on Day 2 (when this kitten was showing signs of toxicity). Four Group A kittens (females #871, #880 and #882, and

male #893) had values of "2" on day 1. None of the Group B kittens had any food consumption value other than "1" for Day 1, but two (female #866 & male #887) had a value of "2" on Day 2.

G. HEMATOLOGY

Group A Kitten #893 (signs of toxicity on Days 1-3) had an increase in neutrophil count on Day 1 (Day -1: 11.09 x $10^3$/µL; Day 1: 18.94 x $10^3$/µL). Group A kitten #871 (but not #882) also showed an increase in neutrophil count on Day 1 (Day -1: 3.43 x $10^3$/µL; Day 1: 12.68 x $10^3$/µL).

H. CLINICAL CHEMISTRY

Group A kitten #893 (signs of toxicity on Days 1-3) showed significant decreases in phosphorus and calcium (41.9% and 40% respectively) on Day 1 from Day -1 levels. Two additional Group A kittens (#871 & #882) showed slight – but noticeable – decreases in phosphorus and calcium on Day 1 (#871: 27.8% and 8.5% respectively from Day -1 values; #882: 25.8% and 11.7% respectively from Day -1 values), and phosphatase (ALP), and decreases in potassium (K), phosphorus (P) and calcium (Ca).

**TABLE 3a. Selected Hematology and Blood Chemistry Values for #893**

| Kitten + Parameter | Day -7 | Day -1 | Day 1 | Day 22 | Day 35 |
|---|---|---|---|---|---|
| **#893:** | | | | | |
| **Neutrophils** | 8.60 x$10^3$/µL | 11.09x$10^3$/µL | **18.94x$10^3$**/µL | 6.31 x $10^3$/µL | 4.44 x $10^3$/µL |
| **Glucose** | 127 mg/dL | 119 mg/dL | 130 mg/dL | 120 mg/dL | 106 mg/dL |
| **Potassium (K)** | 5.7 mmol/L | 6.5 mmol/L | 5.6 mmol/L | 7.1 mmol/L | 5.0 mmol/L |
| **Phosphorus (P)** | 7.0 mg/dL | 7.4 mg/dL | **4.3** mg/dL | 8.4 mg/dL | 7.3 mg/dL |
| **Calcium (Ca)** | 10.7 mg/dL | 11.5 mg/dL | **6.9** mg/dL | 10.9 mg/dL | 10.4 mg/dL |
| **ALP** | 85 u/L | 98 u/L | **51** u/L | 124 u/L | 104 u/L |
| **AST** | 21 u/L | 29 u/L | 25 u/L | 30 u/L | 18 u/L |
| **ALT** | 26 u/L | 36 u/L | 33 u/L | 44 u/L | 42 u/L |

Data from information on p. 81 of MRID 47089405.

Group A female #882, with no signs of toxicity following Day 0 exposure, did have slight decreases in potassium, phosphorus, calcium and alkaline phosphatase activity on Day 1, but there was no biologically significant change in any of the other parameters.

**TABLE 3b. Selected Hematology and Blood Chemistry Values for #882**

| Kitten + Parameter | Day -7 | Day -1 | Day 1 | Day 22 | Day 35 |
|---|---|---|---|---|---|
| **#882:** | | | | | |
| **Neutrophils** | 15.83 x$10^3$/µL | 11.33x$10^3$/µL | 8.35 x$10^3$/µL | 7.84 x $10^3$/µL | 8.44 x $10^3$/µL |
| **Glucose** | 123 mg/dL | 128 mg/dL | 103 mg/dL | 136 mg/dL | 112 mg/dL |
| **Potassium (K)** | 5.5 mmol/L | 5.9 mmol/L | **4.5** mmol/L | 5.0 mmol/L | 5.4 mmol/L |
| **Phosphorus (P)** | 9.9 mg/dL | 9.7 mg/dL | **7.2** mg/dL | 9.0 mg/dL | 8.9 mg/dL |
| **Calcium (Ca)** | 10.9 mg/dL | 11.1 mg/dL | **9.8** mg/dL | 10.4 mg/dL | 10.3 mg/dL |
| **ALP** | 94 u/L | 110 u/L | **59** u/L | 119 u/L | 113 u/L |
| **AST** | 25 u/L | 23 u/L | 30 u/L | 28 u/L | 23 u/L |

*Inert ingredient information may be entitled to confidential treatment*

| | | | | | |
|---|---|---|---|---|---|
| **ALT** | 39 u/L | 74 u/L | 78 u/L | 43 u/L | 46 u/L |

Data from information on p. 73 of MRID 47089405.

Group A female #871, with no signs of toxicity following Day 0 exposure, did have slight decreases in potassium, phosphorus, calcium and alkaline phosphatase activity on Day 1, along with an increase in neutrophil count, but there was no biologically significant change in any of the other parameters.

**TABLE 3b. Selected Hematology and Blood Chemistry Values for #871**

| Kitten + Parameter | Day -7 | Day -1 | Day 1 | Day 22 | Day 35 |
|---|---|---|---|---|---|
| **#871:** | | | | | |
| **Neutrophils** | 4.20 x$10^3$/µL | 3.43 x$10^3$/µL | **12.68** x$10^3$/µL | 4.58 x $10^3$/µL | 3.92 x $10^3$/µL |
| **Glucose** | 128 mg/dL | 120 mg/dL | 115 mg/dL | 111 mg/dL | 110 mg/dL |
| **Potassium (K)** | 5.2 mmol/L | 5.6 mmol/L | **4.3** mmol/L | 4.5 mmol/L | 5.9 mmol/L |
| **Phosphorus (P)** | 6.5 mg/dL | 7.6 mg/dL | **5.5** mg/dL | 7.1 mg/dL | 7.1 mg/dL |
| **Calcium (Ca)** | 10.3 mg/dL | 10.7 mg/dL | **9.8** mg/dL | 10.7 mg/dL | 10.5 mg/dL |
| **ALP** | 136 u/L | 148 u/L | **54** u/L | 216 u/L | 173 u/L |
| **AST** | 22 u/L | 24 u/L | 26 u/L | 24 u/L | 19 u/L |
| **ALT** | 26 u/L | 40 u/L | 28 u/L | 44 u/L | 44 u/L |

Data from information on p. 67 of MRID 47089405.

I. NECROPSY FINDINGS

As there were no deaths, there were no necropsies.

## IV. DISCUSSION

In a companion animal safety study (MRID 47089405), there were two groups, each containing 7 male and 7 female kittens (from 7 weeks 5 days to 8 weeks old at first dosing; day -1 bodyweights: males: 1.48-2.14 lbs; females: 1.36-1.92 lbs; source: Liberty Research Inc., Waverly, NY). Kittens in Group A were treated with the proposed formulation without the actives [redacted] at 3X the label exposure rate for solvents (3 x [0.4 – 0.04] mL = ~1.1 mL; this does not correct for [redacted] while kittens in Group B received no treatment and served as controls.

The dose was applied topically on the backside of the head and the neck of each kitten to avoid runoff. Kittens were treated on Days 0, 7, 14 and 21; the proposed label indicates once-a-month treatment, so that each of the kittens in Group A received a cumulative total of 12X of the proposed monthly dosage of the formulation solvents. Kittens in Group B received no exposure to any test material. On Day 13 the heaviest kitten in Group A weighed 2.46 lbs, so none had reached a weight >9 lbs (4.1 kg) which would have resulted in an increase in the 1X dose from 0.36 to 0.72 mL (Day 13 weights were used to set the dosages for Days 14 and 21).

On the days of dosing (Days 0, 7, 14 and 21) each kitten was observed five times, once prior to dosage and then at hourly intervals for four hours after application. Otherwise, clinical observations were made twice a day. Individual daily food consumption was determined visually, using a scoring system (≥75% consumption = 1, 25-75% consumption = 2, ≤25% consumption = 3). The kittens were weighed six times before and during the study (Days -14, -7, -1, 13, 28 and 35). Blood samples were taken on Days -7, -1, 1, 22, and 35. On all collection days, some kittens were rebled due to clotting of the initial sample. Prothrombin time and activated partial thromboplastic time measurements were not done because of the comparatively large amount of blood required for these tests and the age of the kittens; this protocol deviation had been previously discussed with and accepted by the Agency.

There were no mortalities, as all kittens survived to the termination of the study on Day 35. One Group A male (#893) showed signs (unsteadiness, tremors) of toxicity on Days 1-3; this kitten also showed significant decreases in phosphorus and calcium (41.9% and 40% respectively) on Day 1 from Day -1 levels. Kitten #893 also showed an increase in neutrophil count on Day 1 (Day -1: 11.09 x $10^3$/µL; Day 1: 18.94 x $10^3$/µL). Kitten #893 had no littermates in either Group A or B.

Two additional Group A kittens (#871 & #882) showed slight – but noticeable – decreases in phosphorus and calcium on Day 1 (#871: 27.8% and 8.5% respectively from Day -1 values; #882: 25.8% and 11.7% respectively from Day -1 values), and kitten #871 (but not #882) also showed an increase in neutrophil count on Day 1 (Day -1: 3.43 x $10^3$/µL; Day 1: 12.68 x $10^3$/µL).

A number of kittens (6 in Group A and 4 in Group B) had soft (loose) stools and/or diarrhea in the period from 1 to 6 days after the first dosage.

Following treatment on Day 7 Group A kitten #882 showed depression, slowness and dehydration. However, this kitten had diarrhea on Days 5 through 7; following the day 7 treatment #882 continued to show soft stools/diarrhea through Day 20. This kitten was treated for diarrhea and dehydration on days 7 through 9. These effects were not considered to be related to exposure to the test material.

Group A kittens all showed a rough hair coat (localized effect?) following applications on Days 0, 7, 14 and 21. This is not considered a toxic effect.

This study is classified as **Supplementary** as a companion animal safety study (OPPTS 870.7200) in 8 week-old kittens, in part because it did not involve actual testing of the proposed formulation with actives. This study was apparently conducted (at least in part) to establish the existence of a 3X safety factor with respect to the normal use application exposure levels of the solvent(s) of the proposed Imidacloprid-Pyriproxyfen formulation and the level at which toxicity occurs. As one of the 14 Group A kittens showed signs of toxicity (including unsteadiness and tremors) on Days 1-3 similar to those observed in kittens exposed to 5.6X or 5X levels of the solvent(s) in other studies (MRIDs 47089401 and 47089403) a 3X margin of safety was not established.

*Inert ingredient information may be entitled to confidential treatment*

**ACUTE TOX ONE-LINERS**

1. **DP BARCODE:** D338710
2. **PC CODES:** N/A (solvents only tested)
3. **CURRENT DATE:** 5 September 2007
4. **TEST MATERIAL:** The proposed product contains Imidacloprid (9.1%) and Pyriproxyfen (0.46%), as well as one or more solvents. What was tested in this study was the formulation (solvent[s] + inerts) without active ingredients, [redacted]

| Study/Species/Lab Study # /Date | MRID | Results | Tox. Cat. | Core Grade |
|---|---|---|---|---|
| Companion animal safety / 8-week old kitten / Intervet Inc, DeSoto, KS / Project ID 75191(150.937) / 19-OCT-2000 | 47089405 | 2 groups, each containing 7M & 7F 8-week old domestic short hair kittens were used. Group A was treated at 3X with the solvents and inerts (no actives) of the proposed formulation on days 0, 7, 14 & 21 while Group B was untreated. All kittens survived the 35-day observation period, although one male showed signs (unsteadiness, tremors) of toxicity on Days 1-3. This kitten showed significant decreases in phosphorus and calcium (41.9% & 40% respectively) on Day 1 from Day -1 levels; also an increase in neutrophil count (Day -1: 11.09 x $10^3/\mu L$; Day 1: 18.94 x $10^3/\mu L$); two additional Group A kittens without symptoms also showed slight decreases in phosphorus & calcium on Day 1, and one showed an increase in neutrophil count. Study does not demonstrate a 3X safety factor for the proposed product. | N/A | S |

**Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived, I = Invalid**

CHILD-RESISTANT PACKAGING REVIEW
Technical Review Branch

IN 05/16/2007 OUT 08/6/2007

RD, TRB, Reviewed by Rosalind L. Gross Rosalind L Gross 08/6/2007

EPA Reg. No. or File Symbol 11556-REA

DP Barcode D338713 see also D341440

Decision # 215319
EPA Petition or EUP No. _____

Date Division Received 04/05/2007

Type Product(s) Insecticide (flea product)

Data Accession No(s). 470894-00 (cover letter), 470894-07, 08, 09, 10
Note this data was submitted to cover EPA Reg No. 11556-REI also

Product Mgr./Chemical Review Mgr/Contact Person RM 01 (Kable Davis)
Division RD

Product Name(s) Advantage Plus 9 for Cats

Company Name(s) Bayer Healthcare LLC

Submission Purpose Review of 4 CRP studies to determine if they are adequate to support CRP certification for retail size of 4 and 6 tube blisters of nonchild-resistant tubes (1ml size and 0.4ml fill level).

Active Ingredient(s), PC code, & % Imidacloprid 9.1%
Pyriproxyfen 0.46%

**Summary of Findings**

The child-resistant packaging, CRP, certification (July 10, 2007) submitted is acceptable. Child Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-07) was a pass according to the child sequential test in 16 CFR 1700.20. Senior Adult Use Effectiveness, SAUE, Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-08) was a pass of the Senior Adult test in 16 CFR 1700.20. Child Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-09) was a pass according to the child sequential test in 16 CFR 1700.20. Senior Adult Use Effectiveness Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-10) was a pass of the Senior Adult test in 16 CFR

1700.20.

**In conclusion all the requirements for CRP have been met for this product. However, the directions on opening the package given to the senior during testing for the 4 and 6 tube blisters must be the same directions given to consumers. These directions are on the label for this product, which was dated July 10, 2007.** Additionally, should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to question the child resistance of the package involved.

Package

The package is a plastic blister with a foil backing containing either 4 or 6 tubes of product. The blister is the child-resistant packaging not the individual tubes.

Toxicity

The toxicity of the product, which contains 9.1% Imidacloprid and 0.46% Pyriproxyfen, is based on toxicity data for a 9.1% Imidacloprid and 0.9% Pyriproxyfen formulation. The acute oral $LD_{50}$ was 1000mg/kg for the female rat and 1283mg/kg for the male rat per MRID 45096904. The female rat acute oral $LD_{50}$ 1000mg/kg was used for purposes of CRP. The toxic or harmful amount for an 11.4 kg child is 11.4g (1000mg/kg x 11.4kg), which is 10.4ml of product (11.4g divided by 1.092g/ml). For a tube with 0.4 ml of product a toxic or harmful amount is 26 tubes. For CRP testing a child failure is 9 tubes per 16 CFR 1700.20. Another acute oral $LD_{50}$ study MRID 470894-11 (9.0% Imidacloprid and 0.48% Pyriproxyfen) was submitted to confirm CRP was required for the product. This study indicates an acute oral $LD_{50}$ 1098mg/kg for the female rat, which means 12.5g or 11.4ml is a toxic or harmful amount for an 11.4kg child. **Therefore a child failure remains 9 tubes per 16 CFR 1700.20.**

Company Data

The company submitted a CRP certification and two Child-Resistant Effectiveness and two Senior Adult Use Effectiveness studies to demonstrate the 4 tube and 6 tube blister cards were child-resistant packaging.

**Child Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-07)** involved giving each child 3 blister cards with 4 tubes (1 ml size tube) each containing 0.4 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. The results were one child failure.

**Senior Adult Use Effectiveness Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-08)** involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing. The results of the study were 100% SAUE.

**Child Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-09)** involved giving each child 2 blister cards with 6 tubes (1 ml size tube) each containing 0.4 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. The results were no child failures.

**Senior Adult Use Effectiveness Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-10)** involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing. The results of the study were 99% SAUE.

Analysis of Data and Conclusion

The CRP certification (July 10, 2007) submitted is acceptable.

**Child Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-07)** involved giving each child 3 blister cards with 4 tubes (1 ml size tube) each containing 0.4 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. The results were 1 child failure, which was a 51 month old male child that accessed 9 blister cavities. Additionally, one child accessed 4 blister cavities, two children accessed 2 blister cavities each, and three children accessed one blister cavity each. There was an error in calculating the age of one male child who was actually 52 months old and not 43 months old. However, the error will not effect the conclusion of the study, that the package is child-resistant. **This study was a pass according to the child sequential test in 16 CFR 1700.20.**

**Senior Adult Use Effectiveness Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-08)** involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing because the test directions given to the seniors called for the use of a cutting tool. The results of the study were 100% SAUE. There was an error in calculating the age of one female who was actual 62 years old and not 67 years old. However, the error will not effect the conclusion of the study that the package is SAUE. **The study is a pass of the Senior Adult test in 16 CFR 1700.20.**

**Child Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-9)** involved giving each child 2 blister cards with 6 tubes (1 ml size tube) each containing 0.4 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. The results were no child failures, but one child accessed 3 blister cavities and two children accessed one blister cavity each. **This study was a pass according to the child sequential test in 16 CFR 1700.20.**

**Senior Adult Use Effectiveness Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-10)** involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing because the test directions given to the seniors called for the use of a pair of scissors. The results of the study were 99% SAUE, one 54 year old female failed during the one minute test period. There was an error in calculating the age of one female who was actual 53 years old and not 52 years old. However, the error will not effect the conclusion of the study that the package is SAUE. **The study is a pass of the Senior Adult test in 16 CFR 1700.20.**

**In conclusion all the requirements for CRP have been met for this product. However, the directions on opening the package given to the senior during testing for the 4 and 6 tube blisters must be the same directions given to consumers. These directions are on the label for this product, which was dated July 10, 2007.** Additionally, should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to question the child resistance of the package involved.

Bayer Studies for CR Blister with Tubes Chart

Imidacloprid 9.1% and Pyriproxyfen 0.46%

| EPA # | Toxic/Harmful Amt | Child Failure | ml in tube | 4 tube blister | | 6 tube blister | | CRP Data | CRP Cert |
|---|---|---|---|---|---|---|---|---|---|
| | | | | SAUE | CRE | SAUE | CRE | | |
| 11556-REL | Acute oral $LD_{50}$ = 1098 mg/kg female rat D338715 EPA Reg No 11556-REA MRID 470894-11 July 2007. Toxic/harmful amount 11.4 kg child = 12.5g=11.4ml | 9 tubes | 1 | 100% | 0 Fail | 99% | 0 Fail | Yes | Ok |
| 11556-REA | Acute oral $LD_{50}$ = 1098 mg/kg female rat D338715 EPA Reg No 11556-REA MRID 470894-11 July 2007. Toxic/harmful amount 11.4 kg child = 12.5g=11.4ml | 9 tubes | 0.4 | 100% | 1 Fail | 99% | 0 Fail | Yes | Ok |
| 11556-REO | Acute oral $LD_{50}$ = 1098 mg/kg female rat D338715 EPA Reg No 11556-REA MRID 470894-11 July 2007. Toxic/harmful amount 11.4 kg child = 12.5g=11.4ml | 9 tubes | 0.8 | Pass | Pass | Pass | Pass | use REL and REA Data | Ok |

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**
**WASHINGTON, D.C. 20460**

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

July 18, 2007

MEMORANDUM

Subject: Advantage® Plus 9 for Cats

EPA File Symbol: 11556-REA
DP Barcode: D338715
PC Code: 129099, 129032

From: Olga Odiott 7/18/07
Acting Acute Toxicity Team Leader
Technical Review Branch
Registration Division (7505P)
Byron T. Backus 7/18/07

To: Kable Davis, RM 01
Insecticide Rodenticide Branch
Registration Division (7505P)

Applicant: Bayer Healthcare LLC

FORMULATION FROM LABEL:

| Active Ingredient(s): | % by wt. |
|---|---|
| Imidacloprid | 9.10 % |
| Pyriproxyfen | 0.46 % |
| Other Ingredient(s): | 90.44 % |
| Total: | 100.0 % |

**ACTION REQUESTED:** The Product Manager requests "review of acute oral LD50 study to determine if it supports product registration".

**BACKGROUND:** Bayer Healthcare LLC submitted an acute oral toxicity study to support the registration of the subject product. Previously the company submitted the complete set of acute toxicity data required for registration and the data was reviewed and accepted. The current study was conducted to confirm that the product must be sold in Child Resistant Packaging.

**RECOMMENDATIONS:** The acute oral LD50 study, MRID 470894-11 has been reviewed and classified as acceptable. The study supports and acute oral toxicity Category III for Advantage® Plus 9 for Cats, EPA File Symbol 11556-REA. Recommendations regarding the CRP requirements will be provided separately.

**LABELING:** Please refer to the 22/Sept/2000 TRB Memo from Hashim, M. for the complete acute toxicity profile and precautionary language for this product.

**Reviewer:** Olga Odiott **Date:** July 17, 2007
**Risk Manager (EPA):** Venus Eagle, RM 01

**STUDY TYPE:** Acute Oral Toxicity – Wistar Han Crl: WI rat
OPPTS 870.1100; OECD 425

**TEST MATERIAL:** Imidacloprid: 9.0%; Pyriproxyfen: 0.48%; Lot/Batch No. BB-06-139-M880-06-05-60; Specific gravity 1.11@ 20C; clear amber liquid

**SYNONYMS:** N/A

**CITATION:** Eigenberg, D.A. An Acute Oral $LD_{50}$ Study in the Rat with M880 Insecticide. Study Number 06-A12-IB. Unpublished study prepared by Bayer CropScience LP. March 6, 2007. MRID 470894-11.

**SPONSOR:** Bayer HealthCare LLC, Animal Health Division, P.O. Box 390, Shawnee, KS 66201

**EXECUTIVE SUMMARY:** In an acute oral toxicity study (MRID 470894-11), seven fasted female (nulliparous and nonpregnant) Wistar rats (from Charles River Lab, Inc. Raleigh, NC) were administered M880 insecticide at doses of 175, 550, and 2000 mg/kg bw via oral gavage. Dose selection was based on the Up and Down Procedure, AOT 425 StatPgm. The animals were eight to eleven weeks of age when dosed and the initial body weight range was 158-215 gm. Animals dosed at the 175 and 550 mg/kg bw level survived the duration of the test and gained weight. The 3 animals dosed at the 2000 mg/kg bw level died or were sacrificed. Clinical signs included gasping, difficulty breathing, red stains, yellow stains, tremors, uncoordinated gait, labored breathing, cold to touch, and moribund condition. Wet ventral stain in a rat dosed at the 2000 mg/kg bw level was the only gross pathology finding.

The acute oral $LD_{50}$ for female rats is estimated as 1098 mg/kg bw (EPA Toxicity Category III).

This study is classified as acceptable. It does satisfy the guideline requirements for an acute oral toxicity study (OPPTS 870.1100; OECD 425) in the rat.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

**RESULTS and DISCUSSION:**

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Tuesday, July 17, 2007, 10:54:38 AM
Data file name: 11556-rea.dat

Last modified: 7/17/2007 9:43:35 AM
Test/Substance: M880 Insecticide in Female Wistar Rats
Test type: Main Test
Limit dose (mg/kg): 2000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 2000, 550, 175, 55, 17.5, 5.5, 1.75

DATA:

| Test Seq. | Animal ID | Dose (mg/kg) | Short-term Result | Long-term Result |
|---|---|---|---|---|
| 1 | IB1 | 175 | O | O |
| 2 | IB2 | 550 | O | O |
| 3 | IB3 | 2000 | X | X |
| 4 | IB4 | 550 | O | O |
| 5 | IB5 | 2000 | X | X |
| 6 | IB6 | 550 | O | O |
| 7 | IB7 | 2000 | X | X |

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.

Stopping criteria met: 5 reversals in 6 tests.

SUMMARY OF LONG-TERM RESULTS:

| Dose | O | X | Total |
|---|---|---|---|
| 175 | 1 | 0 | 1 |
| 550 | 3 | 0 | 3 |
| 2000 | 0 | 3 | 3 |
| All Doses | 4 | 3 | 7 |

Statistical Estimate based on long term outcomes:

**Estimated LD50 = 1098 (Based on an assumed sigma of 0.5).**
**Approximate 95% confidence interval is 550 to 2000.**

**A. Mortality** – As noted above.

**B. Clinical observations** – On the day of dosing animals were observed for clinical signs three times, 30 minutes following dosing and twice within the following 4 hours. After the first day animals were observed once each morning for clinical signs and once each afternoon (except weekends) for mortality. No clinical signs were observed for the rat dosed at the 175 mg/kg bw level. Only 1 of the 3 animals dosed at the 500 mg/kg bw level showed clinical signs which consisted of gasping, difficulty breathing and red stains. Rats dosed at the 2000 mg/kg bw level showed yellow stains, tremors, uncoordinated gait, labored breathing, cold to touch, and moribund condition.

**C. Gross Necropsy** – Wet ventral stain in a rat dosed at the 2000 mg/kg bw level was the only gross pathology finding. This rat was sacrificed moribund the first day of the study.

**D. Reviewer's Conclusions** – This study is classified as acceptable. It satisfies the guideline requirements for an acute oral toxicity study (OPPTS 870.1100; OECD 425) in the rat.
The acute oral $LD_{50}$ for female Wistar rats is estimated as 1098 mg/kg bw (95% CI 550 – 2000); the formulation is in EPA Toxicity Category III by this exposure route.

1. **DP BARCODE:** 338715
2. **PC CODE:** 129099, 129032
3. **CURRENT DATE:** July 18, 2007
4. **TEST MATERIAL: :** Imidacloprid: 9.0%; Pyriproxyfen: 0.48%; Lot/Batch No. BB-06-139-M880-06-05-60; Specific gravity 1.11@ 20C; clear amber liquid

| Study/Species/Lab<br>Study # / Date | MRID | Results | Tox. Cat. | Core Grade |
|---|---|---|---|---|
| Acute oral toxicity/rat<br>Bayer CropScience LP; 17745 South Metcalf; Stilwell, KS, 66085<br>Study Number 06-A12-IB; March 6, 2007 | 47089411 | LD50 =<br>1098 mg/kg/bw | III | A |
| | | | | |

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived

Bayer HealthCare
Animal Health Division

OK

*Via Federal Express*

July 10, 2007

Document Processing Desk (NO REGFEE – Additional Information)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Bayer HealthCare LLC
Animal Health Division
12707 Shawnee Mission Parkway
Shawnee Mission, KS 66216-1846

Attention: Mr. Bo Davis
Registration Division

Subject: Advantage® Plus 9 (File Symbol No. 11556-REA)
Child-Resistant Packaging Certification

Dear Mr. Davis:

I certify that the packaging that will be used for this product meets the standard of 40 CFR 157.32.

Sincerely,

F. Terry McNamara

F. Terry McNamara
Director
Preclinical Development and EPA Regulatory Affairs

FTM:DAS/lt

x:moiij/letters/EPA AdvantagePlus9 2007July10.doc

Bayer HealthCare
Animal Health Division

470894-00

*Via Federal Express*

March 8, 2007

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Bayer HealthCare LLC
Animal Health Division
12707 Shawnee Mission Parkway
Shawnee Mission, KS 66216-1846

Attention: Mr. Tom Harris
Registration Division

Subject: Pending Applications for the Registration of Advantage® Plus 10, 20, 55, and 100 Products (EPA File Symbols 11556-REI, REL, RET, and RGN) for pest control on dogs and Advantage® Plus 9 and 18 Products for pest control on cats (File Symbol Nos. 11556-REA and 11556-REO)

Dear Mr. Harris:

Enclosed with this cover letter are revised draft labeling with appropriate supporting documents for the pending registrations of Bayer's Advantage® Plus products for pest control on cats (EPA Files Symbols 11556-REA, and 11556-REO), and dogs (EPA File Symbols 11556-REI, 11556-REL, 11556-RET, and 11556-RGN). The purpose of this cover letter is to provide an explanatory overview of the submission which may aid in the processing of the enclosed information and respective applications.

The time of the original submission, April 10, 2000, predates PRIA and as pending actions should be "grandfathered." However, we agree to make all six related actions Vol-Pay Actions, and we will pay the appropriate fees.

Briefly, the most significant item previously preventing the registrations was that the products had to be in Child-Resistant Packaging (CRP). The packaging scheme for all six registrations is similar, and the CRP testing data for the various sizes are enclosed. The testing design to satisfy the requirements for all product presentations was developed with the agreement of the Agency's expert, Dr. Rosalind Gross. In addition, to support a 9-week kitten label, the reports on three kitten studies and an overall summary (included in the two kitten/cat product applications) are enclosed. These items are discussed in more detail later.

On April 10, 2000, Bayer HealthCare LLC, Animal Health Division submitted draft labels and appropriate documents for the subject registration actions. The Agency reviewed these documents and responded on a number of items, such as requiring the products to be marketed in Child-Resistant Packaging (CRP). Bayer responded to some of the items, but did not on others. We acknowledge that there has been quite a lag in activity with this action, mostly due to changing marketing focus, and the need to generate Child-Resistant Packaging. However, Bayer Healthcare has renewed interest in these products, and the enclosed and accompanying information is in reply to the Agency's comments and/or to support proposed revisions to the pending actions.

The insecticide formulation is identical for all six products. The six application/products differ in terms of use directions for cats or dogs and/or different dose/container sizes for different sizes of cats and dogs. All of the products control one pest - fleas. These products are similar to the Advantage products (Advantage® 9, EPA Reg. No. 11556-116; Advantage® 18, EPA Reg. No. 11556-118; Advantage® 10, EPA Reg. No. 11556-117; Advantage® 20, EPA Reg. No. 11556-119; Advantage® 55, EPA Reg. No. 11556-120; and Advantage® 100, EPA Reg. No. 11556-122), except a small amount (0.46%) of a very effective insect growth regulator, pyriproxyfen, has been added to enhance efficacy against flea eggs. Whereas Advantage® was efficacious against larval and adult fleas, the new combination product is effective against flea larvae, adult fleas, and flea eggs.

The method of application is the same for all six products and is the same application method as for the currently registered Advantage® products. The insecticide formulation is applied from an individual tube to dogs or

appropriate size. As with the cat products, the outer cardboard box will contain all the appropriate labeling except for directions for use. A leaflet with the complete label text will be inside the box with the appropriate blister package. The presentations are identical as for Bayer's currently registered Advantage® products for dogs (EPA Reg. Nos. 11556-117, -119, -120, -122).

The plan for the packaging has not changed from the original submission of 4/1/2000, except that the blister package has been changed to meet child-resistant packaging standards.

In the previous applications for Advantage® Plus 9 for Cats and Kittens (EPA File Symbol 11556-REA) and for Advantage® Plus 18 for Cats (EPA File Symbol 11556-REO) Bayer did not submit domestic animal safety data for kittens. At the time of submission these studies were underway and being discussed with Agency representatives (cited in the enclosed applications). All of these studies are complete. There are three studies described in 1) Bayer Report No. 75120 with a report amendment – Bayer Report No. 75120-1; 2) Bayer Report No. 75190 with a report amendment – Bayer Report No. 75190-1; and 3) Bayer Report No. 75191 with a report amendment – Bayer Report No. 75191-1. These three kitten safety studies with the report amendments support a 9-week kitten age restriction. The reports and their amendments are included with the application for Advantage® Plus 9 for Cats and Kittens (EPA File Symbol 11556-REA), but the data also support the same label restriction for the Advantage® Plus 18 for Cats (EPA File Symbol 11556-REO).

As earlier related, the insecticide formulation is the same for all six products. Also because the acute toxicity value for the formulation was below the 1500 mg/kg "trigger," and because this is a residential use, the products must be marketed in Child-Resistant Packaging (CRP). To resolve this issue for all six products including that each product is to be marketed in two different presentations – a 4-tube package and a 6-tube package – Bayer representatives, Great Lakes Marketing (a CRP testing facility which Bayer has contracted) and Agency representatives, primarily Dr. Rosalind Gross, have had numerous discussions and meetings. The end results of these efforts are Bayer has developed CRP blister packaging for all tube and dose sizes including both 4-tube blisters and 6-tube blisters for each size. Sixteen reports detailing the CRP testing of these blisters are enclosed in this submission.

In agreement with Dr. Rosalind Gross, for the largest dog size, Advantage® Plus 100 (EPA File Symbol 11556-RGN) with a 4.0 mL dose size, Great Lakes Marketing (GLM) tested both the 4-tube and 6-tube blisters with this size tube filled with 4.0 mL of water. The four reports on this testing – 4.0 mL x 4-tube blister child testing (Bayer Report No. 75909), 4.0 mL x 4-tube blister senior testing (Bayer Report No. 75910), 4.0 mL x 6-tube blister child testing (Bayer Report No. 75911), and 4.0 mL x 6-tube blister senior testing (Bayer Report No. 75912) – are enclosed with the documents for Advantage® Plus 100. No other data are included with this particular application.

In agreement with Dr. Rosalind Gross, for Advantage® Plus 55 (EPA File Symbol 11556-RET) with a 2.5 mL dose size, GLM tested both 4-tube and 6-tube blisters with this size tube filled with 2.5 mL of water. The four reports on this testing – 2.5 mL x 4-tube blister child testing (Bayer Report No. 75905), 2.5 mL x 4-tube blister senior testing (Bayer Report No. 75906), 2.5 mL x 6-tube blister child testing (Bayer Report No. 75907), and 2.5 mL x 6-tube blister senior testing (Bayer Report No. 75908) – are enclosed with the documents for Advantage® Plus 55. No other data are included with this particular application.

As the dose size for Advantage® Plus 9 for Cats and Kittens (EPA File Symbol 11556-REA) and the dose size for Advantage® Plus 10 for Dogs and Puppies (EPA File Symbol 11556-REI) are the same – 0.4 mL – packaged in the 1 mL tubes in the same blisters (including 4-tube and 6-tube blisters), Dr. Rosalind Gross agreed testing these 1 mL tubes filled with 0.4 mL water in 4-tube blisters and 6-tube blisters would satisfy the requirements for both the Advantage® Plus 9 for Cats and the Advantage® Plus 10 for Dogs and Puppies registrations. GLM tested these 4-tube and 6-tube blisters. The four reports on this testing – 0.4 mL in 1 mL tubes x 4-tube blister child testing (Bayer Report No. 75913), 0.4 mL in 1 mL tubes x 4-tube blister senior testing (Bayer Report No. 75914), 0.4 mL in 1 mL tubes x 6-tube blister child testing (Bayer Report No. 75915), and 0.4 mL in 1 mL tubes x 6-tube blister senior testing (Bayer Report No. 75916) – are included with the Advantage® Plus 9 for Cats and Kittens application, but they also support the registration of Advantage® Plus 10 for Dogs and Puppies.

In agreement with Dr. Rosalind Gross for Advantage® Plus 20 for Dogs (EPA File Symbol 11556-REL) with a 1.0 mL dose size in a 1 mL tube, GLM tested both the 4-tube and 6-tube blisters with this size tube filled with 1.0 mL water. The four reports on this testing – 1.0 mL in 1 mL tube x 4-tube blister child testing (Bayer Report No. 75897), 1.0 mL in 1 mL tube x 4-tube blister senior testing (Bayer Report No. 75898), 1.0 mL in 1 mL tube x 6-tube blister child testing (Bayer Report No. 75893), and 1.0 mL in 1 mL tube x 6-tube blister senior testing (Bayer Report No. 75894) – are enclosed with the application for Advantage® Plus 20 for Dogs (EPA File Symbol 11556-REL). No other data are included with this application.

With regard to Advantage® Plus 18 for Cats (EPA File Symbol 11556-REO), this dose size is 0.8 mL filled into 1 mL tubes packaged in 4- and 6-tube blisters. This dose fill is bracketed by the 0.4 mL dose fill of Advantage® Plus 9 for Cats and Kittens and Advantage® Plus10 for Dogs and Puppies and the 1.0 mL dose fill for Advantage® Plus 20 for Dogs in the same packaging scheme. Based on this bracketing, Dr. Gross "was willing to not require testing of the 0.8 mL level if the 50 child sequential test are a high pass (not 5 children at the ten minute mark) for the 1.0 and 0.4 mL fill levels" (12/01/06 e-mail from Dr. Gross to Dr. Lori Dixon of GLM). As the 0.4 mL and 1.0 mL fill level tests were a high pass, Bayer did not test the 0.8 mL dose size. Thus, there are no CRP data, nor any other data enclosed with the application for Advantage® Plus 18 for Cats (EPA File Symbol 11556-REO).

For Advantage® Plus10 (EPA File Symbol 11556-REI) for dogs and puppies, as related above, the CRP testing for this packaging is enclosed with the application for Advantage® Plus 9 (EPA File Symbol 11556-REA). Thus there are no data enclosed with the application for Advantage® Plus10.

Also, with regard to the overall CRP testing of the various packaging configurations, Bayer is aware of PR Notice 97-9 regarding the electronic submission of CRP test data. GLM (representing Bayer in this matter) has contacted Dr. Rosalind Gross of the Agency with regard to the format of such data. These data prepared by GLM and as specified by Dr. Gross will be hand-delivered to Dr. Gross on a CD.

I hope this overview cover letter is helpful in processing the attached applications. If you have any questions, please do not hesitate to call me at (913) 268-2751.

Sincerely,

F. T. McNamara for Douglas Spilker

Douglas A. Spilker. Ph. D.
Manager, EPA Regulatory Affairs

Doug.Spilker.b@Bayer.com

DAS/lt

Enclosures

Transmittal Document

1. Name and Address of Submitter
Bayer HealthCare LLC
Animal Health Division
Box 390
Shawnee Mission, Kansas 66201-0390

M.T. McNamara for Douglas Spilker

Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs
(913) 268-2751

2. Regulatory Action in Which this Package is Submitted
Data submitted to support proposed label claim for Advantage® Plus 9 for Cats (EPA File Symbol 11556-REA)

3. Transmittal Date
March 8, 2007

4. List of Submitted Studies:

| MRID No. | Volume | | |
|---|---|---|---|
| 47089401 | 1 | - | "Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-On Formulation in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75120, A. Abraham, 160 p. |
| 47089402 | 2 | - | "Amendment One: Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-On Formulation in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75120-1, A. Abraham, 5 p. |

| | | | |
|---|---|---|---|
| **47089403** | 3 | - | "Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 5.0% Water Blank Formulation in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75190, A. Abraham, 165 p. |
| **47089404** | 4 | - | "Amendment One: Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 5.0% Water Blank Formulation in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75190-1, A. Abraham, 5 p. |
| **47089405** | 5 | - | "Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 4.6% Water Blank Formulation at Three Times the Use Rate Volume in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75191, A. Abraham, 133 p. |
| **47089406** | 6 | - | "Amendment One: Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 4.6% Water Blank Formulation at Three Times the Use Rate Volume in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75191-1, A. Abraham, 5 p. |
| **47089407** | 7 | - | "Child-Resistant Packaging (CRP) Child Panel Test of 4 x 0.4 mL Advantage® Plus PVC Blisters for Dogs and Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No. 75913, L. M. Dixon, 57 p. |
| **47089408** | 8 | - | "Child-Resistant Packaging (CRP) Senior Adult Panel Test of 4 x 0.4 ml Advantage® Plus PVC Blisters for Dogs and Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No. 75914, L. M. Dixon, 240 p. |
| **47089409** | 9 | - | "Child-Resistant Packaging (CRP) Child Panel Test of 6 x 0.4 mL Advantage® Plus PVC Blisters for Dogs and Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No. 75915, L. M. Dixon, 58 p. |

| | | | |
|---|---|---|---|
| **47089410** | 10 | - | "Child-Resistant Packaging (CRP) Senior Adult Panel Test of 6 x 0.4 mL Advantage® Plus PVC Blisters for Dogs and Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No.75916, L. M. Dixon, 239 p. |
| **47089411** | 11 | - | "An Acute Oral $LD_{50}$ Study in the Rat with M880 Insecticide," EPA Guideline No. 870.1100, Bayer Report No. 75922, D. A. Eigenberg, 34 p. |

# ATTACHMENT FOR OPP
# APPLICATION FOR PESTICIDE NOTIFICATION

Advantage® Plus 9 for Cats

With this application form and the enclosed documents, Bayer HealthCare, Animal Health Division, requests the registration of Advantage® Plus 9 for Cats (EPA File Symbol No. 11556-REA), a new insecticide product.

On April 10, 2000, Bayer HealthCare LLC, Animal Health Division, submitted draft labels and appropriate documents for the subject registration action. The Agency reviewed the applications and provided a number of responses. Bayer responded to some of the items but not all. We acknowledge that there has been a significant time delay on Bayer's part in responding on this matter, mostly due to a changing marketing focus, and the need to generate Child-Resistant Packaging. However, Bayer HealthCare has renewed interest in this product, and the enclosed and accompanying information are in reply to the Agency's comments and/or to support proposed revisions to the pending action. The following is a current overview of the pending action, and how Bayer is meeting current registration requirements:

Status of Registration Package and Remaining Requirements for
Bayer HealthCare, Animal Health Division's Advantage® Plus 9 for Cats
(EPA File Symbol 11556-REA)

Briefly, this product will consist of a blister package constructed of plastic and foil containing individual plastic tubes each containing 0.4 ml of the liquid insecticide. There will be two package sizes – a 4-tube package and a 6-tube package. The plastic and foil blisters will be marketed inside cardboard boxes. The boxes will contain all of the draft labeling text, dated 03/01/07, which is enclosed (5 copies each), except for the directions for use. The complete label text, including directions for use, will be in a leaflet insert that will accompany the blister package in the cardboard box. The individual plastic tubes inside the blisters will contain only the draft labeling indicated on page 9 of the label text, again dated 03/01/07, which is enclosed (5 copies each). Please note, because the tubes are very small in size, we are proposing that only the product name, the active ingredients, the amounts of the active ingredients and the EPA Reg. No. be printed onto each tube. Also note, this packaging and labeling scheme is identical to that used by Bayer's currently registered product, Advantage® 9 for Cats (EPA Reg. No. 11556-116). The plan for the packaging has not changed from the original submission of 4/1/2000, except that the aforementioned blister package has been modified and will now meet child-resistant packaging standards (discussed later).

*Product ingredient source information may be entitled to confidential treatment*

**Product Labeling**

Enclosed for Agency acceptance are five (5) copies each of two draft labels (4-pack and 6-pack sizes), dated 03/01/07, for Advantage® Plus 9 for Cats (EPA File Symbol 11556-REA). Please note that the 4-pack and 6-pack labels are identical except for the net contents statement. The enclosed draft labeling is to replace the label submitted to the Agency on April 10, 2000 (label dated April 7, 2000). The new enclosed label includes the following changes:

1. Addition of appropriate label language to propose a minimum age restriction (9-weeks) on kittens;
2. Broadening the bulleted list of marketing claims;
3. Replacing the long chemical names with common chemical names, with the respective CAS numbers, in the active ingredient statement;
4. Reordering of the elements of the FIRST AID Statement;
5. Adding the English volume units, as required;
6. Updating the Bayer HealthCare corporate name and address; as well as appropriately revising the name in the Warranty Statement;
7. Revising the HOW TO APPLY section to include more information since the product will now be sold in Child-Resistant Packaging.

**Product Chemistry**

The insecticide formulation is a liquid solution of imidacloprid (9.1% w/w) and pyriproxyfen (0.46% w/w) in inert ingredients which are on EPA's list of acceptable inert ingredients for use in pesticides. The source of the active ingredients for this product are NTN 33893 Technical, EPA Reg. No. 264-755 (formerly 3125-414), and [redacted] The product chemistry data to support the registration of this new formulation are in the following Bayer Reports which were submitted to EPA with the original application for registration on April 10, 2000:

Bayer Report No. 75133 entitled "Product Chemistry of (10% w/v, 9.1% w/w) Imidacloprid + (0.5% w/v, 0.46% w/w) Pyriproxyfen Topical Solution – OPPTS 830 – Group A: Product Identity, Composition, and Analysis," EPA MRID No. 45096902,

Bayer Report No. 75132 entitled "Product Chemistry of (10% w/v, 9.1% w/w) Imidacloprid + (0.5% w/v, 0.46% w/w) Pyriproxyfen Water Topical Solution, OPPTS 830 Group B – Physical/Chemical Properties," EPA MRID No. 45096903, and,

Bayer Report No. 75130 entitled "Validation of Bayer Animal Health Test Method TMC-14.02 for the Determination of Imidacloprid and Pyriproxyfen Topical Solution Formulation by HPLC," EPA MRID No. 45096901.

Although the report titles do not use the "Advantage® Plus" trade name, the formulation described and tested is Advantage® Plus 9 for Cats.

Also, these three product chemistry reports support the registration of the five other Advantage® Plus products [Advantage® Plus 18 for Cats (EPA File Symbol 11556-REO), and Advantage® Plus 10 for Dogs and Puppies (EPA File Symbol 11556-REI), Advantage® Plus 20 for Dogs (EPA File Symbol 11556-REL), Advantage® Plus 55 for Dogs (EPA File Symbol 11556-RET), and Advantage® Plus 100 for Dogs (EPA File Symbol 11556-RGN)] whose applications are accompanying this application.

The Agency reviewed these product chemistry data (review dated June 2, 2000), and sent this to Bayer with a June 16, 2000 cover letter. The review identified some deficiencies. Bayer responded to the deficiencies in an October 27, 2000 letter. The Agency reviewed this response in a November 22, 2000 review document provided to Bayer with a January 12, 2001 cover letter. The Agency agreed that all product chemistry requirements, except for the two following items, have been fulfilled:

1. **Storage Stability** – Bayer agrees that a storage stability study is required, and Bayer will provide these data. As it is necessary to obtain storage stability information using final packaging, registrants routinely use product manufactured during the first production run after registration for the stability study. Therefore, we will conduct a storage stability study after registration and once production has commenced.

2. **Nominal Concentration of Active Ingredients** – As suggested by the Agency, we have allowed for an adjustment to the level of each active ingredient used in the formulation based on the purity of the technical. This allows the nominal concentration of each active ingredient on the Confidential Statement of Formula (CSF) to be identical to the concentration on the draft labels submitted with this application. Corrected CSF's were submitted on April 12, 2001 (CSF's dated April 11, 2001) that reflect these changes to the active ingredient levels.

With the submission of revised CSF's on April 12, 2001 and the agreement to conduct a storage stability study using manufactured end-use product in its final packaging, Bayer has satisfied the Agency's requirements for the product chemistry for the Advantage® Plus products (EPA File Symbols 11556-REO, -REA, REI, -REL, -RET, -RGN).

Please note, as the EPA Registration Number for NTN 33983 Technical (Imidacloprid) has subsequently changed from 3125-414 to 264-755, we are enclosing two copies of a revised CSF for Advantage® Plus 9, dated March 8, 2007. The only changes in the enclosed CSF are this change in EPA Registration Number, the change in our company name, and the change in the EPA product manager to Tom Harris from Tina Levine.

**Product Toxicology**

To support the registration of Advantage® Plus 9 (and also for the other five Advantage® Plus products), the following acute toxicology data were submitted with the original applications for registration sent April 10, 2000.

| EPA MRID Number | EPA Guideline Number | Bayer Report Number | Bayer Report Title |
|---|---|---|---|
| 45096904 | 870.1100 | 75195 | Acute Oral Toxicity Study with Imidacloprid (9.1%) /Pyriproxyfen (0.9%) Spot On in Rats |
| 45096905 | 870.1200 | 75196 | Acute Dermal Toxicity Study with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in Rats |
| 45096906 | 870.1300 | 75197 | Acute 4-Hour Inhalation Toxicity Study with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in Rats |
| 45096907 | 870.2400 | 75199 | Primary Eye Irritation Study in Rabbits with Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On |
| 45096908 | 870.2500 | 75200 | Primary Dermal Irritation Study in Rabbits with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On |
| 45096909 | 870.2600 | 75201 | Dermal Sensitization Study in Guinea Pigs – Closed Patch Technique with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On |

Please note, the study titles refer to test materials with a slightly different formulation than that which is proposed for registration. The formulation proposed for registration contains 9.1% imidacloprid, 0.46% pyriproxyfen, and [redacted] and the other inert ingredients identified on the Confidential Statement of Formula. The formulation used for five of the acute toxicity studies contained 9.1% imidacloprid and a higher pyriproxyfen concentration (0.9%) [redacted] The formulation used for the primary eye irritation study (Bayer Report No. 75199, EPA MRID No. 45096907) contained 9.1% imidacloprid, 0.9% pyriproxyfen, [redacted] (please note the study title states [redacted] the formulation was [redacted] as documented in the Confidential Appendix to Report No. 75199). In a November 2, 1999 meeting between EPA and Bayer representatives, the Agency's technical reviewers (Byron Backus and John Redden) confirmed that EPA would accept these studies since the formulation tested represents a "worst case" compared to the current formulation proposed for registration.

The Agency reviewed these six studies (review dated August 30, 2000 provided to Bayer with a September 7, 2000 cover letter). All six studies were classified as "Acceptable" by the Agency and have fulfilled the acute toxicology requirements necessary for registration. Based on the results of these six acute toxicity studies, the Agency has concluded that the product will be a Toxicity Category III product with a CAUTION signal word. The enclosed draft labeling reflects this signal word.

The results of the acute oral toxicity study (EPA MRID No. 45096904) were an $LD_{50}$ of 1283 mg/kg for male rats and 1000 mg/kg for female rates. As these values were below the 1500 mg/kg threshold level, and as this is a residential use, the Agency specified the product must be in child-resistant packaging (CRP). Bayer has now conducted a follow-up acute oral toxicity study (Bayer Report No. 75922; enclosed with this application) with the proposed final end-use formulation (9.1% imidacloprid, 0.46% pyriproxyfen, and [redacted] to confirm if this product must be in child-resistant packaging. The estimated oral $LD_{50}$ for female rats in this study is 1098 mg/kg, and again below the 1500 mg/kg threshold for child-resistant packaging. Therefore, we understand that the Advantage® Plus products must be sold in child-resistant packaging (CRP) to receive registration from the Agency. Data from CRP testing is enclosed with this action and is discussed below.

**Child-Resistant Packaging Testing**

Various Bayer Animal Health representatives and various Agency representatives, particularly Dr. Rosalind Gross, have had numerous meetings and telephone conversations to discuss this issue. Based on the package design of plastic tubes filled with individual doses enclosed in plastic and foil blister packages, Dr. Gross advised that either the plastic tubes, the blister package for the tubes, or both must be Child-Resistant. Bayer conducted Child-Resistant package testing on the tubes, and the tubes failed. Bayer then focused our efforts on developing a Child Resistant blister packaging to hold the tubes. The blister packages containing plastic tubes filled with 0.4 ml water (necessary for testing liability reasons) were then tested. As there will be two different size blisters – one for the 4-tube package and one for the 6-tube package – both blister sizes were tested. The Child-Resistant Packaging tests have been conducted by Great Lakes Marketing, Toledo, Ohio, using both children and senior panel tests according to the Agency guidance and the effectiveness specifications in 16 CFR Part 1700.15 (b) for child-resistant (special) packaging. Details of the child-resistant and senior adult panel tests for both the 4-tube blister and 6-tube blister packages are included in the following enclosed reports to support the registration of Advantage® Plus 9 for Cats:

Bayer Report No. 75913 entitled "Child-Resistant Packaging (CRP) Child Panel Test of 4 x 0.4 ml Advantage Plus PVC Blisters for Dogs and Cats"

Bayer Report No. 75914 entitled "Child-Resistant Packaging (CRP) Senior Adult Panel Test of 4 x 0.4 ml Advantage Plus PVC Blisters for Dogs and Cats"

Bayer Report No. 75915 entitled "Child-Resistant Packaging (CRP) Child Panel Test of 6 x 0.4 ml Advantage Plus PVC Blisters for Dogs and Cats"

Bayer Report No. 75916 entitled "Child-Resistant Packaging (CRP) Senior Adult Panel Test of 6 x 0.4 ml Advantage Plus PVC Blisters for Dogs and Cats"

The results of these studies demonstrate that the blister packages for both the 4- and 6-tube sizes are Child-Resistant. The tubes in these studies were filled with 0.4 ml of water. This is the exact fill volume and packaging proposed for Advantage® Plus 9 for Cats.

Also please note, the 0.4 ml fill volume in plastic tubes packaged in these 4-tube and 6-tube blisters is the same packaging presentations proposed for Advantage® Plus 10 for Dogs and Puppies (EPA File Symbol 11556-REI). Therefore, the above listed studies also support the registration of Advantage® Plus 10 for Dogs and Puppies (EPA File Symbol 11556-REI).

**Efficacy**

To support the claim of flea control for the Advantage® Plus 9 (and 18) product(s) on cats, Bayer is citing studies previously submitted to, reviewed by, and accepted by the Agency for Bayer's currently registered Advantage® 9 for Cats (EPA Reg. No. 11556-116) and Advantage® 18 for Cats (EPA Reg. No. 11556-118) products. Specifically, these reports are:

EPA MRID 43679503 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Cats" (Bayer Report No. 74571) and,

EPA MRID 43679504 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Cats" (Bayer Report No. 74581).

EPA MRID 43679609 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Dogs" (Bayer Report No. 74572) and,

EPA MRID 43679610 entitled "Efficacy Confirmation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Dogs" (Bayer Report No. 74541).

The above referenced studies support the once-per-month use of imidacloprid (Advantage®) to control fleas and, therefore, the once-per-month use of imidacloprid in Advantage® Plus to control fleas.

The currently accepted labels for Advantage® 9 and 18 for Cats and the draft proposed labels for Advantage® Plus 9 and 18 for Cats have a claim for water resistance of the product, larvicidal efficacy, and a 12-hour "speed of kill" claim. These claims are supported by Bayer studies previously submitted to, reviewed by, and accepted by the Agency for Bayer's currently registered products Advantage® 9 for Cats (EPA Reg. No. 11556-116) and Advantage® 18 for Cats (EPA Reg. No. 11556-118). Specifically, these reports are:

EPA MRID 44256903 entitled "Evaluation of the Effects of Shampooing or Water Immersion on the Initial and Residual Efficacy of Advantage® for Flea Control on Dogs" (Bayer Report No. 74792),

EPA MRID 44256902 entitled "Imidacloprid Topical Formulation: Larvicidal Effect Against *Ctenocephalides felis* in the Surroundings of Treated Dogs" (Bayer Report No. 74828) and,

EPA MRID 44256901 entitled "Comparative Evaluation of How Quickly Advantage® and Frontline™ (fipronil) Top Spot Kill Fleas on Dogs" (Bayer Report No. 74800).

Whereas Advantage® was efficacious against larval and adult fleas, the new Advantage® Plus product is effective against flea larvae, adult fleas, and flea eggs. The active ingredient, pyriproxyfen, is currently registered in at least 92 products for many different uses. Among these registrations, there are at least 13 currently registered pyriproxyfen flea products which range in active ingredient concentration from 0.125 to 5.3 percent. The concentration of pyriproxyfen in Advantage® Plus (0.46%) falls within the range of concentrations of the currently registered products.

In Bayer's original application for registration (April 10, 2000), Bayer cited four efficacy studies with pyriproxyfen from McLaughlin Gormley King Co. (MGK), but MGK did not yet know the MRID Nos. for the studies. Bayer is now citing three efficacy studies from MGK with the appropriate MRID No. Enclosed with these applications is an authorization letter from MGK to permit the use of these data to support the Advantage® Plus products. Specifically, these reports are:

EPA MRID No. 450860801 entitled "Evaluation of Two Concentrations of Nylar (Pyriproxyfen) in a Dip and Shampoo Formulation Against the Hatch of Flea Eggs Collected from Treated Cats" (MGK Report No. OT018-94),

EPA MRID No. 450860801 "Flea Eggs: Target of the New IGR On-Animal Treatments" (MGK Report No. OT016-93),

EPA MRID No. 450860801 "Final Report on Comparison of Isopropyl Alcohol Dilutions of Pyriproxyfen and Fenoxycarb on Hatchability of Flea Eggs" (MGK Report No. OT006-96) and,

Please note that "Nylar" is a trade name for pyriproxyfen.

The results of these studies support the once-a-month application rate for Advantage® Plus since the efficacious concentration of pyriproxyfen used in the studies was lower than the concentration in the formulation proposed for registration. In addition, the lower concentration of pyriproxyfen was shown to be effective for a period greater than one month.

These efficacy study reports also support the registration of the other Advantage® Plus product for cats - Advantage® Plus 18 for Cats - whose application accompanies this application.

## Domestic Animal Safety

### Adult Cats

In the original submission for registration (April 10, 2000), Bayer submitted Bayer Report 75122 (*Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-on Formulation in the Target Species, Adult Cats*) to demonstrate the safety of Advantage Plus 9 for Cats and Kittens in adult cats. The report was assigned EPA MRID No. 45097001 and underwent Agency review. The EPA concluded that the report was "Acceptable" and that the study adequately addressed the safety requirements contained in Guideline 870.7200: *Companion Animal Safety.*

Furthermore, the aforementioned report (EPA MRID No. 45097001) also supports the pending registration of ADVANTAGE® PLUS 18 for Cats. The application for registration of ADVANTAGE® PLUS 18 accompanies this submission.

### Kittens

A series of three companion animal studies collectively demonstrated the safety of ADVANTAGE® PLUS (both 9 and 18) in kittens **9 weeks** of age and older. The individual design of these studies and the results were discussed by Bayer and Agency representatives. A brief summary of study histories and results is presented below:

On June 8, 1999, Bayer and EPA representatives met to discuss data requirements for the registration of ADVANTAGE® PLUS [at that time, the formulation was 9.1% imidacloprid with 0.9% pyriproxyfen (PPF)]. After these discussions, acute toxicity and companion animal safety studies were initiated. Based on results from the eye irritation study, the 9.1% imidacloprid + 0.9% PPF formulation met the criteria of Toxicity Category I. Therefore, in an effort to reduce ocular/corneal irritation, and as the original formulation was known to be hygroscopic (absorbs and retains water), [redacted] was added resulting in the modified formulation used in another eye irritation study (EPA MRID No. 45096907). Afterwards the PPF concentration was also lowered to 0.46%, and this final formulation with [redacted] and a lower level of PPF is what is proposed for registration.

In the initial kitten safety study (Bayer study 150.851), two groups of 14 kittens (7 males and 7 females), 8-weeks-old at first treatment, were topically treated once weekly for four consecutive weeks, either with 2.0 ml (5X label dose) of 9.1% imidacloprid + 0.9% PPF or with 2.0 ml of pure vehicle minus active ingredients (as the active ingredients represented 10% of this formulation, then 5X dose of vehicle minus actives = 1.8 ml; therefore the 2.0 ml vehicle used in the study is actually equivalent to 5.6X label dose). Treatments with 9.1% imidacloprid + 0.9% PPF represented a cumulative 20X monthly label dose whereas treatments with vehicle minus active ingredients actually represented a cumulative 22.4X (4 x 5.6X) monthly dose. Throughout the entire study, treatment-related clinical signs were not observed in kittens dosed with 9.1% imidacloprid + 0.9% PPF. Conversely, neurological signs (including depression, generalized tremors, pupillary constriction/dilation) were observed in four kittens treated with 5.6X vehicle

minus active ingredients: Two 8-week-old kittens (#783, #791) developed tremors and died on the day following the first treatment. Another kitten (#776) developed neurological signs following both the second and third vehicular treatments but recovered without therapy (kitten was 9 and 10 weeks old at the second and third treatments, respectively). Lastly, a fourth kitten (#788) exhibited generalized tremors but also recovered without therapy following the fourth treatment (kitten was 11 weeks old) with 5.6X vehicle minus actives. Profuse salivation, suggestive of oral exposure to the vehicle, was observed prior to the onset of neurological signs in two (#776, #783) of four kittens. In both kittens that had died, cellular necrosis was observed microscopically in the external granular layer of the cerebellum.

Based on this study, one would conclude that the formulated product was safe at 5X in 8-week-old kittens, but that the vehicle caused adverse effects at a 5.6X dose, particularly in 8-week kittens.

Bayer notified the Agency of these untoward results with a letter (October 20, 1999) followed by discussions in Washington, DC (November 2, 1999) with Agency representatives. Bayer and the Agency concurred that treatment of kittens (8 weeks old at initial treatment) with 2.0 ml (5X label dose) of 9.1% imidacloprid + 0.9% PPF, once weekly for four consecutive weeks, was not associated with adverse post-treatment effects. Bayer proposed to conduct a new kitten safety study but with the reformulated product which is now being proposed for registration: 9.1% imidacloprid + 0.46% PPF + [redacted] As the vehicle without actives was more toxic than the actual formulation with actives, Bayer and EPA both agreed that it would only be necessary to evaluate the reformulated vehicle in the new safety study. [Note: 9.1% imidacloprid + 0.9% PPF (the original formulation) was also found to be more toxic than 9.1% imidacloprid + 0.9% PPF + [redacted] (reformulation) in the acute eye irritation study.] Furthermore, it was agreed that 1.8 ml of vehicle (new formulation minus imidacloprid and PPF) would satisfactorily represent a true 5X dose and that kittens, 8 weeks old at first treatment, would be topically dosed once weekly for 4 consecutive weeks with 1.8 ml of the reformulated vehicle minus actives.

In the second kitten safety study (Bayer study 150.828), 16 kittens (8 males and 8 females), 8 weeks old at first treatment, were topically treated once weekly for four consecutive weeks with 1.8 ml (5X) of vehicle. An additional 16 kittens (8 males and 8 females), 8 weeks old at first treatment, were maintained as untreated controls. Similar to the first study (Bayer study 150.851), two 8-week-old kittens (#811, #816) developed severe neurological signs on the day following the first treatment. Both kittens were subsequently euthanized in the afternoon of that day. Transient salivation, suggestive of oral exposure to the vehicle, was observed in one kitten (#811) shortly after treatment application. In both euthanized kittens, cellular necrosis was observed microscopically in the external granular layer of the cerebellum. In addition, mild neurological signs were observed in a third kitten (#814) following application of the second treatment (kitten was 9 weeks old). This kitten recovered without therapy. Treatment related adverse clinical signs were not observed at any time throughout the study in the remaining 13 treated kittens.

In a third kitten safety study (Bayer study 150.937), 14 kittens (7 males and 7 females), 8 weeks old at first treatment, were topically treated once weekly for four consecutive weeks with 1.1 ml (3X label dose) of vehicle. An additional 14 kittens (7 males and 7 females), 8 weeks old at first

treatment, were maintained as untreated controls. Following the first treatment application, one kitten (#893) developed mild neurological signs, but recovered without therapy. Treatment related adverse clinical signs were not observed at any time throughout the study in the remaining 13 treated kittens.

The results from these three studies are summarized in the attached table and were discussed with Agency representatives, after transmittal via facsimile (February 15, 2000), on February 17, 2000.

**Table 1**

| Study No. | Formulation Used | Dose (use rate) | Number of Kittens Affected | | | |
|---|---|---|---|---|---|---|
| | | | 8 Weeks of Age 1st Dose | 9 Weeks of Age 2nd Dose | 10 Weeks of Age 3rd Dose | 11 Weeks of Age 4th Dose |
| 150.851 | 9.1% imidacloprid with 0.9% pyriproxyfen spot-on | 5X (2 ml) | 0/14 | 0/14 | 0/14 | 0/14 |
| | Vehicle (no actives) | 5.6X (2 ml)* | 2/14[1] | 1/12[2] | 1/12[2] | 1/12[3] |
| 150.828 | Vehicle (no actives) from the new formulation | 5X (1.8 ml) | 2/16[4] | 1/14[5] | 0/14 | 0/14 |
| 150.937 | Vehicle (no actives) from the new formulation | 3X (1.1 ml) | 1/14[6] | 0/14 | 0/14 | 0/14 |

*2 mL vehicle is equivalent to 5.6X product as the product was 10% active ingredient; 2mL product = 5X = 0.2 mL active ingredients + 1.8 mL vehicle.

[1] = Two kittens (#783 and 791) developed neurological signs and died following treatment.
[2] = One kitten (# 776) developed mild neurological signs after the 2nd and 3rd treatments. This kitten fully recovered from both episodes without therapy.
[3] = One kitten (#778) developed mild neurological signs after the 4th treatment. This kitten fully recovered without therapy.
[4] = Two kittens (#811, 816) developed severe neurological signs and were euthanized.
[5] = One kitten (#814) developed mild neurological signs after the second treatment, but recovered fully without therapy.
[6] = One kitten (#893) developed mild neurological signs after the first treatment, but recovered fully without therapy.

In conclusion, no significant treatment-related clinical signs were observed in fourteen 8-week-old kittens (first treatment) following the topical administration of 5X the original formulation (9.1% imidacloprid + 0.9% PPF), once weekly, for four consecutive weeks (20X the monthly label dose). However, the topical administration of 5.6X formulation minus actives (vehicle) resulted in the death of two 8-week-old kittens, and transient, self-resolving neurological signs in

one kitten following both the second and third treatments (9 and 10 weeks of age) and in a second kitten following the fourth treatment (11 weeks of age). The formulation was subsequently modified to include [redacted] resulting in reduced toxicity based on results from the acute eye irritation studies. [The PPF concentration was also subsequently lowered to 0.46%, and an acute oral toxicity study was done with this final formulation (Bayer Report No. 75922, enclosed with this application). The acute LD50 value from the initial formulation was 1000 mg/kg in female rats while the estimated LD50 value in the new study with the final formulation was 1098 mg/kg in female rats.] Following discussions with Agency representatives, the safety of the reformulated vehicle was subsequently evaluated in 30 additional 8-week-old kittens. Severe neurological signs, resulting in humane euthanasia, were observed in two 8-week-old kittens treated with 5X the vehicle. Also, mild, self-resolving post-treatment neurological signs were observed in **one** 9-week-old kitten **(5X)** and in **one** 8-week-old kitten **(3X)** following topical administration of the vehicle. No other adverse treatment-related clinical signs were noted in the remaining 26 kittens at any time, including after treatment at 8 weeks of age. Thus, if one considers only the 9-week kitten data from these studies, there were no treatment related effects with 5X the formulation, there was one kitten affected but resolved at 5.6X vehicle, one kitten affected but resolved at 5X vehicle, and no kittens affected at 3X vehicle. Moreover the repeated weekly overdosing conducted in these studies constitutes a severe test of safety. Considering this extensive amount of data, and the demonstrated safety of the formulation at 20X the label dose, this product is safe for use in kittens and cats 9 weeks of age and older.

Enclosed for Agency review are three (3) copies of each report and three (3) copies of each report amendment for three domestic animal safety studies which support the revised minimum age restriction. Specifically, these are:

1) "Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-On Formulation in the Target Species, Eight Week Old Kittens," (Bayer Report Number 75120 on Bayer study 150.851)

This is the study report on the first kitten study.

2) "Amendment One: Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-On Formulation in the Target Species, Eight Week Old Kittens," (Bayer Report Number 75120-1)

This is an amendment of the first report to correct the title page for the confidential attachment of the original report and more importantly provide the composition of the placebo (in a confidential appendix).

3) "Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 5.0% Water Blank Formulation in the Target Species, Eight Week Old Kittens" (Bayer Report Number 75190 on Bayer study 150.828)

This is the report on the second kitten study.

4) "Amendment One: Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 5.0% Water Blank Formulation in the Target Species, Eight Week Old Kittens" (Bayer Report Number 75190-1)

This is an amendment of the second report to correct the completion date on the title page of the report, to correct the title page of the confidential appendix, and to correct the placebo composition information.

5) "Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 4.6% Water Blank Formulation at Three Times the Use Rate Volume in the Target Species, Eight Week Old Kittens" (Bayer Report Number 75191 on Bayer study 150.937)

This is the report on the third kitten study.

6) "Amendment One: Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 4.6% Water Blank Formulation at Three Times the Use Rate Volume in the Target Species, Eight Week Old Kittens" (Bayer Report Number 75191-1).

This is an amendment of the third report to correct the completion date from 'TBD" to October 19, 2000 on the report title page and confidential attachment title page, and to correct the placebo composition information.

**Data Compensation**

An appropriate data matrix listing all of the data necessary to support the registration of Advantage® Plus 9 (and also Advantage® Plus 18, the other Advantage® Plus product for cats) is enclosed with this application. Please note, the enclosed data matrix cites only those data necessary for this registration. This registration application is for a product used only on cats (classified as an indoor, non-food use); the data matrix does not cite any imidacloprid environmental fate, ecological effects nor residue chemistry data because these data are not necessary for this proposed registration.

**Generic Data**

With regard to **imidacloprid,** Bayer CropScience LP (BCS) is the basic registrant of imidacloprid. BCS and Bayer HealthCare LLC (BHC) are wholly owned subsidiaries of Bayer Corporation, and therefore, the BHC, Animal Health Division, cannot claim Formulator's Exemption for the generic data requirements. Accordingly, enclosed is a copy of Letter of Authorization from Bayer CropScience (EPA Company No. 264) authorizing the use of the generic imidacloprid data by Bayer HealthCare LLC, Animal Health Division (EPA Company No. 11556). These generic data are cited in the enclosed data matrix.

With regard to pyriproxyfen, a completed Formulator's Exemption form (EPA Form 8570-27) was enclosed with the initial application for Bayer to address compensation of pyriproxyfen generic data. Also, enclosed with the initial application was a Letter of Authorization from Sumitomo Chemical Company Ltd. These documents are still appropriate.

**Product Specific Data**

All of the data necessary to support the registration of Advantage® Plus 9 are data previously submitted by Bayer's Animal Health group (EPA Company No. 11556) or are enclosed with this application or were submitted by the McLaughlin Gormley King Co. (MGK). Enclosed with this application is a Letter of Authorization from MGK. All of these data are cited in the enclosed data matrix.

With the original application for registration (April 10, 2000), we provided completed Certification With Respect to Citation of Data (EPA Form 8570-29) indicating we are choosing the Selective Method of Support for pyriproxyfen efficacy data. Again, a Letter of Authorization from MGK to cite these data is enclosed. These documents are still appropriate.

# Bayer HealthCare
## Animal Health Division

*Via Federal Express*

July 10, 2007

Document Processing Desk (NO REGFEE – Additional Information)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Bayer HealthCare LLC
Animal Health Division
12707 Shawnee Mission Parkway
Shawnee Mission, KS 66216-1846

Attention: Mr. Bo Davis
Registration Division

Subject: Advantage® Plus 9 (File Symbol No. 11556-REA)
Child-Resistant Packaging Certification

Dear Mr. Davis:

I certify that the packaging that will be used for this product meets the standard of 40 CFR 157.32.

Sincerely,

F. Terry McNamara

F. Terry McNamara
Director
Preclinical Development and EPA Regulatory Affairs

FTM:DAS/lt

x:moiij/letters/EPA AdvantagePlus9 2007July10.doc

# Bayer HealthCare
## Animal Health Division

*Via Federal Express*

July 10, 2007

Document Processing Desk (NO REGFEE – Additional Information)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
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Arlington, VA 22202-4501

Attention: Mr. Bo Davis - Registration Division

Subject: Pending Applications for the Registration of Advantage® Plus 10, 20, 55, and 100 Products (EPA File Symbols 11556-REI, REL, RET, and RGN) for pest control on dogs and Advantage® Plus 9 and 18 Products for pest control on cats (File Symbol Nos. 11556-REA and 11556-REO)

Bayer HealthCare LLC
Animal Health Division
12707 Shawnee Mission Parkway
Shawnee Mission, KS 66216-1846

Dear Mr. Davis:

Pursuant to 40 CFR 157.34, "The registrant of a pesticide product required to be in child-resistant packaging shall certify to the Agency that the package meets the standards of § 157.32."

The subject pending applications for registration are for products which will be required to be in child-resistant packaging. Accordingly, please find enclosed with this cover letter six separate CRP certification letters for the respective subject products.

If you have any questions, please do not hesitate to call me at (913) 268-2751.

Sincerely,

Douglas A. Spilker. Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker.b@Bayer.com

DAS/lt

Enclosures: Six Certification Letters

x:moiij/letters/EPA AdvantagePlus2007July10.doc

Bayer HealthCare
Animal Health Division

470894-00

*Via Federal Express*

March 8, 2007

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Bayer HealthCare LLC
Animal Health Division
12707 Shawnee Mission Parkway
Shawnee Mission, KS 66216-1846

Attention: Mr. Tom Harris
Registration Division

Subject: Pending Applications for the Registration of Advantage® Plus 10, 20, 55, and 100 Products (EPA File Symbols 11556-REI, REL, RET, and RGN) for pest control on dogs and Advantage® Plus 9 and 18 Products for pest control on cats (File Symbol Nos. 11556-REA and 11556-REO)

Dear Mr. Harris:

Enclosed with this cover letter are revised draft labeling with appropriate supporting documents for the pending registrations of Bayer's Advantage® Plus products for pest control on cats (EPA Files Symbols 11556-REA, and 11556-REO), and dogs (EPA File Symbols 11556-REI, 11556-REL, 11556-RET, and 11556-RGN). The purpose of this cover letter is to provide an explanatory overview of the submission which may aid in the processing of the enclosed information and respective applications.

The time of the original submission, April 10, 2000, predates PRIA and as pending actions should be "grandfathered." However, we agree to make all six related actions Vol-Pay Actions, and we will pay the appropriate fees.

Briefly, the most significant item previously preventing the registrations was that the products had to be in Child-Resistant Packaging (CRP). The packaging scheme for all six registrations is similar, and the CRP testing data for the various sizes are enclosed. The testing design to satisfy the requirements for all product presentations was developed with the agreement of the Agency's expert, Dr. Rosalind Gross. In addition, to support a 9-week kitten label, the reports on three kitten studies and an overall summary (included in the two kitten/cat product applications) are enclosed. These items are discussed in more detail later.

On April 10, 2000, Bayer HealthCare LLC, Animal Health Division submitted draft labels and appropriate documents for the subject registration actions. The Agency reviewed these documents and responded on a number of items, such as requiring the products to be marketed in Child-Resistant Packaging (CRP). Bayer responded to some of the items, but did not on others. We acknowledge that there has been quite a lag in activity with this action, mostly due to changing marketing focus, and the need to generate Child-Resistant Packaging. However, Bayer Healthcare has renewed interest in these products, and the enclosed and accompanying information is in reply to the Agency's comments and/or to support proposed revisions to the pending actions.

The insecticide formulation is identical for all six products. The six application/products differ in terms of use directions for cats or dogs and/or different dose/container sizes for different sizes of cats and dogs. All of the products control one pest - fleas. These products are similar to the Advantage products (Advantage® 9, EPA Reg. No. 11556-116; Advantage® 18, EPA Reg. No. 11556-118; Advantage® 10, EPA Reg. No. 11556-117; Advantage® 20, EPA Reg. No. 11556-119; Advantage® 55, EPA Reg. No. 11556-120; and Advantage® 100, EPA Reg. No. 11556-122), except a small amount (0.46%) of a very effective insect growth regulator, pyriproxyfen, has been added to enhance efficacy against flea eggs. Whereas Advantage® was efficacious against larval and adult fleas, the new combination product is effective against flea larvae, adult fleas, and flea eggs.

The method of application is the same for all six products and is the same application method as for the currently registered Advantage® products. The insecticide formulation is applied from an individual tube to dogs or

appropriate size. As with the cat products, the outer cardboard box will contain all the appropriate labeling except for directions for use. A leaflet with the complete label text will be inside the box with the appropriate blister package. The presentations are identical as for Bayer's currently registered Advantage® products for dogs (EPA Reg. Nos. 11556-117, -119, -120, -122).

The plan for the packaging has not changed from the original submission of 4/1/2000, except that the blister package has been changed to meet child-resistant packaging standards.

In the previous applications for Advantage® Plus 9 for Cats and Kittens (EPA File Symbol 11556-REA) and for Advantage® Plus 18 for Cats (EPA File Symbol 11556-REO) Bayer did not submit domestic animal safety data for kittens. At the time of submission these studies were underway and being discussed with Agency representatives (cited in the enclosed applications). All of these studies are complete. There are three studies described in 1) Bayer Report No. 75120 with a report amendment – Bayer Report No. 75120-1; 2) Bayer Report No. 75190 with a report amendment – Bayer Report No. 75190-1; and 3) Bayer Report No. 75191 with a report amendment – Bayer Report No. 75191-1. These three kitten safety studies with the report amendments support a 9-week kitten age restriction. The reports and their amendments are included with the application for Advantage® Plus 9 for Cats and Kittens (EPA File Symbol 11556-REA), but the data also support the same label restriction for the Advantage® Plus 18 for Cats (EPA File Symbol 11556-REO).

As earlier related, the insecticide formulation is the same for all six products. Also because the acute toxicity value for the formulation was below the 1500 mg/kg "trigger," and because this is a residential use, the products must be marketed in Child-Resistant Packaging (CRP). To resolve this issue for all six products including that each product is to be marketed in two different presentations – a 4-tube package and a 6-tube package – Bayer representatives, Great Lakes Marketing (a CRP testing facility which Bayer has contracted) and Agency representatives, primarily Dr. Rosalind Gross, have had numerous discussions and meetings. The end results of these efforts are Bayer has developed CRP blister packaging for all tube and dose sizes including both 4-tube blisters and 6-tube blisters for each size. Sixteen reports detailing the CRP testing of these blisters are enclosed in this submission.

In agreement with Dr. Rosalind Gross, for the largest dog size, Advantage® Plus 100 (EPA File Symbol 11556-RGN) with a 4.0 mL dose size, Great Lakes Marketing (GLM) tested both the 4-tube and 6-tube blisters with this size tube filled with 4.0 mL of water. The four reports on this testing – 4.0 mL x 4-tube blister child testing (Bayer Report No. 75909), 4.0 mL x 4-tube blister senior testing (Bayer Report No. 75910), 4.0 mL x 6-tube blister child testing (Bayer Report No. 75911), and 4.0 mL x 6-tube blister senior testing (Bayer Report No. 75912) – are enclosed with the documents for Advantage® Plus 100. No other data are included with this particular application.

In agreement with Dr. Rosalind Gross, for Advantage® Plus 55 (EPA File Symbol 11556-RET) with a 2.5 mL dose size, GLM tested both 4-tube and 6-tube blisters with this size tube filled with 2.5 mL of water. The four reports on this testing – 2.5 mL x 4-tube blister child testing (Bayer Report No. 75905), 2.5 mL x 4-tube blister senior testing (Bayer Report No. 75906), 2.5 mL x 6-tube blister child testing (Bayer Report No. 75907), and 2.5 mL x 6-tube blister senior testing (Bayer Report No. 75908) – are enclosed with the documents for Advantage® Plus 55. No other data are included with this particular application.

As the dose size for Advantage® Plus 9 for Cats and Kittens (EPA File Symbol 11556-REA) and the dose size for Advantage® Plus 10 for Dogs and Puppies (EPA File Symbol 11556-REI) are the same – 0.4 mL – packaged in the 1 mL tubes in the same blisters (including 4-tube and 6-tube blisters), Dr. Rosalind Gross agreed testing these 1 mL tubes filled with 0.4 mL water in 4-tube blisters and 6-tube blisters would satisfy the requirements for both the Advantage® Plus 9 for Cats and the Advantage® Plus 10 for Dogs and Puppies registrations. GLM tested these 4-tube and 6-tube blisters. The four reports on this testing – 0.4 mL in 1 mL tubes x 4-tube blister child testing (Bayer Report No. 75913), 0.4 mL in 1 mL tubes x 4-tube blister senior testing (Bayer Report No. 75914), 0.4 mL in 1 mL tubes x 6-tube blister child testing (Bayer Report No. 75915), and 0.4 mL in 1 mL tubes x 6-tube blister senior testing (Bayer Report No. 75916) – are included with the Advantage® Plus 9 for Cats and Kittens application, but they also support the registration of Advantage® Plus 10 for Dogs and Puppies.

In agreement with Dr. Rosalind Gross for Advantage® Plus 20 for Dogs (EPA File Symbol 11556-REL) with a 1.0 mL dose size in a 1 mL tube, GLM tested both the 4-tube and 6-tube blisters with this size tube filled with 1.0 mL water. The four reports on this testing – 1.0 mL in 1 mL tube x 4-tube blister child testing (Bayer Report No. 75897), 1.0 mL in 1 mL tube x 4-tube blister senior testing (Bayer Report No. 75898), 1.0 mL in 1 mL tube x 6-tube blister child testing (Bayer Report No. 75893), and 1.0 mL in 1 mL tube x 6-tube blister senior testing (Bayer Report No. 75894) – are enclosed with the application for Advantage® Plus 20 for Dogs (EPA File Symbol 11556-REL). No other data are included with this application.

With regard to Advantage® Plus 18 for Cats (EPA File Symbol 11556-REO), this dose size is 0.8 mL filled into 1 mL tubes packaged in 4- and 6-tube blisters. This dose fill is bracketed by the 0.4 mL dose fill of Advantage® Plus 9 for Cats and Kittens and Advantage® Plus10 for Dogs and Puppies and the 1.0 mL dose fill for Advantage® Plus 20 for Dogs in the same packaging scheme. Based on this bracketing, Dr. Gross "was willing to not require testing of the 0.8 mL level if the 50 child sequential test are a high pass (not 5 children at the ten minute mark) for the 1.0 and 0.4 mL fill levels" (12/01/06 e-mail from Dr. Gross to Dr. Lori Dixon of GLM). As the 0.4 mL and 1.0 mL fill level tests were a high pass, Bayer did not test the 0.8 mL dose size. Thus, there are no CRP data, nor any other data enclosed with the application for Advantage® Plus 18 for Cats (EPA File Symbol 11556-REO).

For Advantage® Plus10 (EPA File Symbol 11556-REI) for dogs and puppies, as related above, the CRP testing for this packaging is enclosed with the application for Advantage® Plus 9 (EPA File Symbol 11556-REA). Thus there are no data enclosed with the application for Advantage® Plus10.

Also, with regard to the overall CRP testing of the various packaging configurations, Bayer is aware of PR Notice 97-9 regarding the electronic submission of CRP test data. GLM (representing Bayer in this matter) has contacted Dr. Rosalind Gross of the Agency with regard to the format of such data. These data prepared by GLM and as specified by Dr. Gross will be hand-delivered to Dr. Gross on a CD.

I hope this overview cover letter is helpful in processing the attached applications. If you have any questions, please do not hesitate to call me at (913) 268-2751.

Sincerely,

F. J. McNamara for Douglas Spilker

Douglas A. Spilker. Ph. D.
Manager, EPA Regulatory Affairs

Doug.Spilker.b@Bayer.com

DAS/lt

Enclosures

Transmittal Document

1. Name and Address of Submitter
Bayer HealthCare LLC
Animal Health Division
Box 390
Shawnee Mission, Kansas 66201-0390

M.T. McNamara for Douglas Spilker

Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs
(913) 268-2751

2. Regulatory Action in Which this Package is Submitted
Data submitted to support proposed label claim for Advantage® Plus 9 for Cats (EPA File Symbol 11556-REA)

3. Transmittal Date
March 8, 2007

4. List of Submitted Studies:

| MRID No. | Volume | | |
|---|---|---|---|
| **47089401** | 1 | - | "Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-On Formulation in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75120, A. Abraham, 160 p. |
| **47089402** | 2 | - | "Amendment One: Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-On Formulation in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75120-1, A. Abraham, 5 p. |

| | | | |
|---|---|---|---|
| **47089403** | 3 | - | "Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 5.0% Water Blank Formulation in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75190, A. Abraham, 165 p. |
| **47089404** | 4 | - | "Amendment One: Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 5.0% Water Blank Formulation in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75190-1, A. Abraham, 5 p. |
| **47089405** | 5 | - | "Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 4.6% Water Blank Formulation at Three Times the Use Rate Volume in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75191, A. Abraham, 133 p. |
| **47089406** | 6 | - | "Amendment One: Evaluation of the General Safety of 9.1% Imidacloprid with 0.45% Pyriproxyfen Spot-On with 4.6% Water Blank Formulation at Three Times the Use Rate Volume in the Target Species, Eight Week Old Kittens," EPA Guideline No. 870-7200, Bayer Report No. 75191-1, A. Abraham, 5 p. |
| **47089407** | 7 | - | "Child-Resistant Packaging (CRP) Child Panel Test of 4 x 0.4 mL Advantage® Plus PVC Blisters for Dogs and Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No. 75913, L. M. Dixon, 57 p. |
| **47089408** | 8 | - | "Child-Resistant Packaging (CRP) Senior Adult Panel Test of 4 x 0.4 ml Advantage® Plus PVC Blisters for Dogs and Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No. 75914, L. M. Dixon, 240 p. |
| **47089409** | 9 | - | "Child-Resistant Packaging (CRP) Child Panel Test of 6 x 0.4 mL Advantage® Plus PVC Blisters for Dogs and Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No. 75915, L. M. Dixon, 58 p. |

| | | | |
|---|---|---|---|
| **47089410** | 10 | - | "Child-Resistant Packaging (CRP) Senior Adult Panel Test of 6 x 0.4 mL Advantage® Plus PVC Blisters for Dogs and Cats," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No.75916, L. M. Dixon, 239 p. |
| **47089411** | 11 | - | "An Acute Oral $LD_{50}$ Study in the Rat with M880 Insecticide," EPA Guideline No. 870.1100, Bayer Report No. 75922, D. A. Eigenberg, 34 p. |

# Bayer CropScience

February 28, 2007

Document Processing Desk
Office of Pesticide Programs (7505P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, Virginia 22202-4501

Attention: Mr. Tom Harris (PM 01, RD)

**Re: Letter of Authorization: Imidacloprid**
**Bayer HealthCare LLC, Animal Health Division (BHC) –**
**Advantage® Plus Application for Registration**

Bayer CropScience
2 T.W. Alexander Drive
P. O. Box 12014
Research Triangle Park,
NC 27709
Tel: 919 549-2000

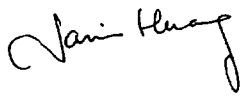
Dear Mr. Harris,

Bayer CropScience LP (BCS) hereby authorizes the Agency to refer to any research and/or test data on our active ingredient imidacloprid (the active ingredient in ADMIRE® and PROVADO®) in support of the applications for registration of **Advantage® Plus 9** (EPA File Symbol: 11556-REA), **Advantage® Plus 18** (EPA File Symbol: 11556-REO), **Advantage® Plus 10** (EPA File Symbol: 11556-REI), **Advantage® Plus 20** (EPA File Symbol: 11556-REL), **Advantage® Plus 55** (EPA File Symbol: 11556-RET) and **Advantage® Plus 100** (EPA File Symbol: 11556-RGN), submitted by Bayer HealthCare LLC, Animal Health Division (BHC), P.O. Box 390, Shawnee Mission, KS, 66201-0390.

Furthermore, BCS and BHC are wholly owned subsidiaries of Bayer Corporation. Both companies seek product registrations for products containing the active ingredient imidacloprid. Any confidential business information released by the Agency in data evaluation records or other documents for company number 264 can be disclosed without restriction to the BHC, company number 11556. In addition, the Agency is authorized to refer to any research and/or test data submitted under company number 264 in support of applications for registration from Bayer HealthCare LLC, Animal Health Division (BHC), company number 11556.

Please contact me at jamin.huang@bayercropscience.com or at 919-549-2634 if you have any questions regarding this submission.

Sincerely,



Jamin Huang, Ph.D.
Product Registration Manager

CC: Doug Spilker, Ph.D., Bayer HealthCare LLC, Animal Health Division

Print Form

*Please read instructions on reverse before completing form.* Form Approved. OMB No. 2070-0060. Approval expires 2-28-

United States
**Environmental Protection Agency**
Washington, DC 20460

[X] **Registration**
[ ] **Amendment**
[ ] **Other**

OPP Identifier Number

U18

## Application for Pesticide - Section I

| 1. Company/Product Number | 2. EPA Product Manager | 3. Proposed Classification |
|---|---|---|
| 11556-REA | Tom Harris | [X] None [ ] Restricted |
| **4. Company/Product (Name)** | **PM#** | |
| Advantage Plus 9 for Cats | Acting PM1 | |

**5. Name and Address of Applicant** *(Include ZIP Code)*
Bayer HealthCare LLC, Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

[ ] *Check if this is a new address*

**6. Expedited Reveiw.** In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to:
EPA Reg. No. _____
Product Name _____

## Section - II

[ ] Amendment - Explain below.
[ ] Resubmission in response to Agency letter dated _____
[ ] Notification - Explain below.
[ ] Final printed labels in repsonse to Agency letter dated _____
[ ] "Me Too" Application.
[X] Other - Explain below.

**Explanation:** Use additional page(s) if necessary. (For section I and Section II.)

Non-fast Track Amendment (review of data); Proposed fee category: R34, CR No. 89. Action: Modification of the Label. Justification: Although this action is pending & should be grandfathered-in, we agree to a Vol-Pay Action. See attached for additional explanation.

## Section - III

**1. Material This Product Will Be Packaged In:**

| Child-Resistant Packaging | Unit Packaging | Water Soluble Packaging | 2. Type of Container |
|---|---|---|---|
| [X] Yes [ ] No | [ ] Yes [X] No | [ ] Yes [X] No Text | [ ] Metal [X] Plastic [ ] Glass [X] Paper [ ] Other (Specify) _____ |
| * Certification must be submitted | If "Yes" Unit Packaging wgt. / No. per container | If "Yes" Package wgt / No. per container | |

| 3. Location of Net Contents Information | 4. Size(s) Retail Container | 5. Location of Label Directions |
|---|---|---|
| [X] Label [ ] Container | 4/6-0.4 mL tubes | [ ] On Label [X] On Labeling accompaning product |

**6. Manner in Which Label is Affixed to Product** [ ] Lithograph [ ] Paper glued [ ] Stenciled [X] Other See attachment

## Section - IV

**1. Contact Point** *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

| Name | Title | Telephone No. (Include Area Code) |
|---|---|---|
| Douglas A. Spilker (doug.spilker.b@bayer.com) | EPA Regulatory Manager | 913-268-2751 |

**Certification**

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowlingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

**6. Date Application Received** (Stamped)

| 2. Signature | 3. Title |
|---|---|
| M. J. McNamara for Douglas Spilker | EPA Regulatory Manager |
| **4. Typed Name** | **5. Date** |
| Douglas A. Spilker | March 8, 2007 |

*Page 133 Confidential Statement of Formula may be entitled to confidential treatment*